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(54) **GENETIC VARIANTS ON CHR 11Q AND 6Q AS MARKERS FOR PROSTATE AND COLORECTAL CANCER PREDISPOSITION**

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CPC ***C12Q 1/6886*** (2013.01); *C12Q 2600/156* (2013.01)
USPC **435/6.11**

(58) **Field of Classification Search**
None
See application file for complete search history.

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(57) **ABSTRACT**

It has been discovered that certain polymorphic markers on chromosome 6 and chromosome 11 are indicative of a susceptibility to prostate cancer and colon cancer. The invention describes diagnostic applications for determining a susceptibility to cancer using such markers, as well as kits for use in such applications.

35 Claims, 1 Drawing Sheet

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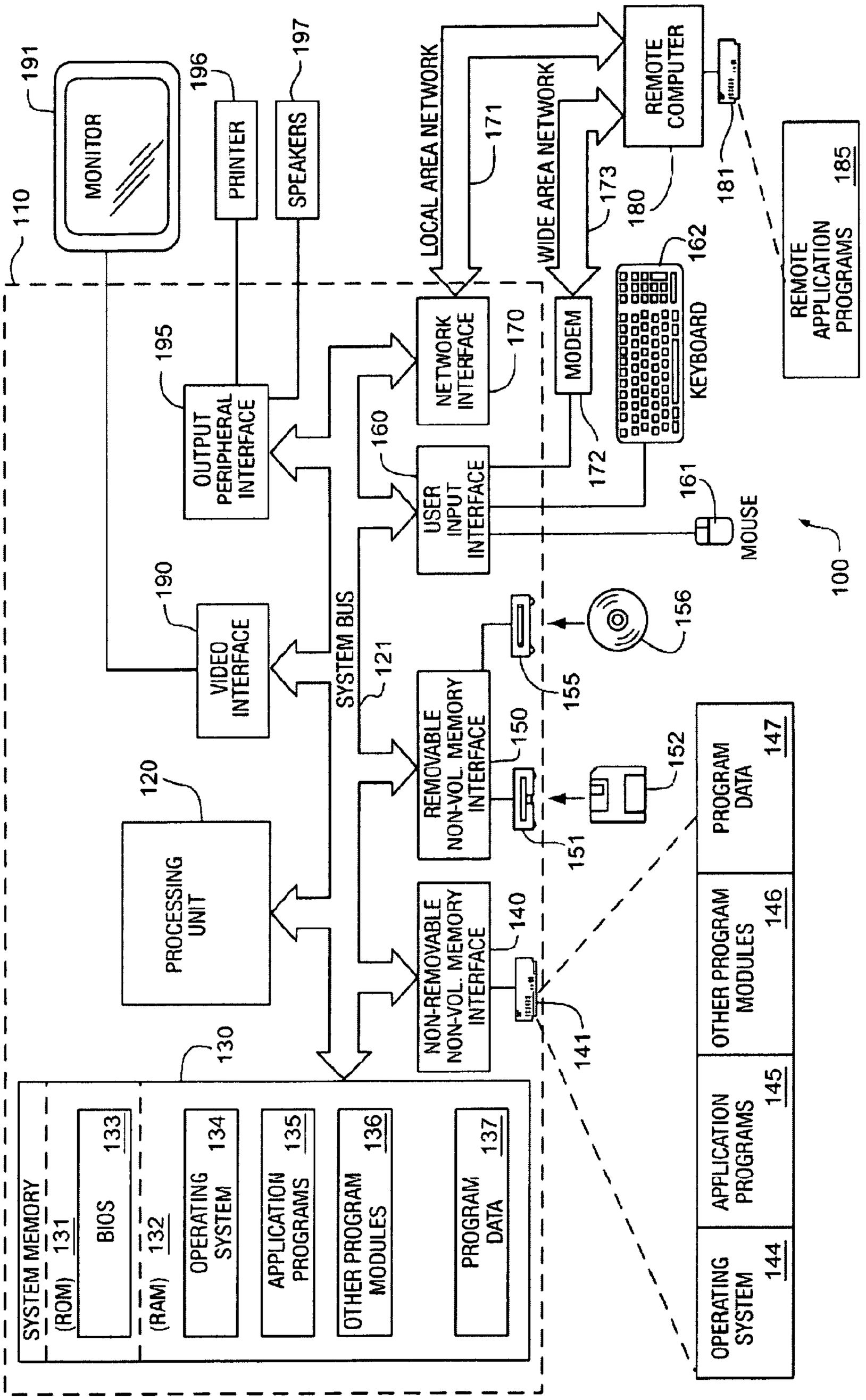
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GENETIC VARIANTS ON CHR 11Q AND 6Q AS MARKERS FOR PROSTATE AND COLORECTAL CANCER PREDISPOSITION

RELATED APPLICATION

This application claims priority under 35 U.S.C. §119 or 365 to Iceland, Application No. 8696, filed Nov. 30, 2007. The entire teachings of the above application are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Cancer, the uncontrolled growth of malignant cells, is a major health problem of the modern medical era and is one of the leading causes of death in developed countries. In the United States, one in four deaths is caused by cancer (Jemal, A. et al., *CA Cancer J. Clin.* 52:23-47 (2002)).

The incidence of prostate cancer has dramatically increased over the last decades and prostate cancer is now a leading cause of death in the United States and Western Europe (Peschel, R. E. and J. W. Colberg, *Lancet* 4:233-41 (2003); Nelson, W. G. et al., *N. Engl. J. Med.* 349(4):366-81 (2003)). Prostate cancer is the most frequently diagnosed noncutaneous malignancy among men in industrialized countries, and in the United States, 1 in 8 men will develop prostate cancer during his life (Simard, J. et al., *Endocrinology* 143 (6):2029-40 (2002)). Although environmental factors, such as dietary factors and lifestyle-related factors, contribute to the risk of prostate cancer, genetic factors have also been shown to play an important role. Indeed, a positive family history is among the strongest epidemiological risk factors for prostate cancer, and twin studies comparing the concordant occurrence of prostate cancer in monozygotic twins have consistently revealed a stronger hereditary component in the risk of prostate cancer than in any other type of cancer (Nelson, W. G. et al., *N. Engl. J. Med.* 349(4):366-81 (2003); Lichtenstein P. et. al., *N. Engl. J. Med.* 343(2):78-85 (2000)). In addition, an increased risk of prostate cancer is seen in 1^{st} to 5^{th} degree relatives of prostate cancer cases in a nation wide study on the familiality of all cancer cases diagnosed in Iceland from 1955-2003 (Amundadottir et. al., *PLoS Medicine* 1(3):e65 (2004)). The genetic basis for this disease, emphasized by the increased risk among relatives, is further supported by studies of prostate cancer among particular populations: for example, African Americans have among the highest incidence of prostate cancer and mortality rate attributable to this disease: they are 1.6 times as likely to develop prostate cancer and 2.4 times as likely to die from this disease than European Americans (Ries, L. A. G. et al., *NIH Pub. No.* 99-4649 (1999)).

An average 40% reduction in life expectancy affects males with prostate cancer. If detected early, prior to metastasis and local spread beyond the capsule, prostate cancer can be cured (e.g., using surgery). However, if diagnosed after spread and metastasis from the prostate, prostate cancer is typically a fatal disease with low cure rates. While prostate-specific antigen (PSA)-based screening has aided early diagnosis of prostate cancer, it is neither highly sensitive nor specific (Punglia et. al., *N Engl J Med.* 349(4):335-42 (2003)). This means that a high percentage of false negative and false positive diagnoses are associated with the test. The consequences are both many instances of missed cancers and unnecessary follow-up biopsies for those without cancer. As many as 65 to 85% of individuals (depending on age) with prostate cancer have a PSA value less than or equal to 4.0 ng/mL, which has traditionally been used as the upper limit for a normal PSA level

(Punglia et. al., *N Engl J Med.* 349(4):335-42 (2003); Cookston, M. S., *Cancer Control* 8(2):133-40 (2001); Thompson, I. M. et. al., *N Engl J Med.* 350:2239-46 (2004)). A significant fraction of those cancers with low PSA levels are scored as Gleason grade 7 or higher, which is a measure of an aggressive prostate cancer.

In addition to the sensitivity problem outlined above, PSA testing also has difficulty with specificity and predicting prognosis. PSA levels can be abnormal in those without prostate cancer. For example, benign prostatic hyperplasia (BPH) is one common cause of a false-positive PSA test. In addition, a variety of noncancer conditions may elevate serum PSA levels, including urinary retention, prostatitis, vigorous prostate massage and ejaculation.

Subsequent confirmation of prostate cancer using needle biopsy in patients with positive PSA levels is difficult if the tumor is too small to see by ultrasound. Multiple random samples are typically taken but diagnosis of prostate cancer may be missed because of the sampling of only small amounts of tissue. Digital rectal examination (DRE) also misses many cancers because only the posterior lobe of the prostate is examined. As early cancers are nonpalpable, cancers detected by DRE may already have spread outside the prostate (Mistry K. J., *Am. Board Fam. Pract.* 16(2):95-101 (2003)).

Thus, there is clearly a great need for improved diagnostic procedures that would facilitate early-stage prostate cancer detection and prognosis, as well as aid in preventive and curative treatments of the disease. In addition, there is a need to develop tools to better identify those patients who are more likely to have aggressive forms of prostate cancer from those patients that are more likely to have more benign forms of prostate cancer that remain localized within the prostate and do not contribute significantly to morbidity or mortality. This would help to avoid invasive and costly procedures for patients not at significant risk.

The incidence of prostate cancer has dramatically increased over the last decades. Prostate cancer is a multifactorial disease with genetic and environmental components involved in its etiology. It is characterized by heterogeneous growth patterns that range from slow growing tumors to very rapid highly metastatic lesions.

Although genetic factors are among the strongest epidemiological risk factors for prostate cancer, the search for genetic determinants involved in the disease has been challenging. Studies have revealed that linking candidate genetic markers to prostate cancer has been more difficult than identifying susceptibility genes for other cancers, such as breast, ovary and colorectal cancer. Several reasons have been proposed for this increased difficulty including: the fact that prostate cancer is often diagnosed at a late age thereby often making it difficult to obtain DNA samples from living affected individuals for more than one generation; the presence within high-risk pedigrees of phenocopies that are associated with a lack of distinguishing features between hereditary and sporadic forms; and the genetic heterogeneity of prostate cancer and the accompanying difficulty of developing appropriate statistical transmission models for this complex disease (Simard, J. et al., *Endocrinology* 143(6):2029-40 (2002)).

Various genome scans for prostate cancer-susceptibility genes have been conducted and several prostate cancer susceptibility loci have been reported. For example, HPC1 (1q24-q25), PCAP (1q42-q43), HCPX (Xq27-q28), CAPB (1p36), HPC20 (20q13), HPC2/ELAC2 (17p11) and 16q23 have been proposed as prostate cancer susceptibility loci (Simard, J. et al., *Endocrinology* 143(6):2029-40 (2002); Nwosu, V. et al., *Hum. Mol. Genet.* 10(20):2313-18 (2001)).

In a genome scan conducted by Smith et al., the strongest evidence for linkage was at HPC1, although two-point analysis also revealed a LOD score of ≥1.5 at D4S430 and LOD scores ≥1.0 at several loci, including markers at Xq27-28 (Ostrander E. A. and J. L. Stanford, *Am. J. Hum. Genet.* 67:1367-75 (2000)). In other genome scans, two-point LOD scores of ≥1.5 for chromosomes 10q, 12q and 14q using an autosomal dominant model of inheritance, and chromosomes 1q, 8q, 10q and 16p using a recessive model of inheritance, have been reported, as well as nominal evidence for linkage to chr 2q, 12p, 15q, 16q and 16p. A genome scan for prostate cancer predisposition loci using a small set of Utah high risk prostate cancer pedigrees and a set of 300 polymorphic markers provided evidence for linkage to a locus on chromosome 17p (Simard, J. et al., *Endocrinology* 143(6):2029-40 (2002)). Eight new linkage analyses were published in late 2003, which depicted remarkable heterogeneity. Eleven peaks with LOD scores higher than 2.0 were reported, none of which overlapped (see Actane consortium, Schleutker et. al., Wiklund et. al., Witte et. al., Janer Xu et. al., Lange et. al., Cunningham et al.; all of which appear in *Prostate*, vol. 57 (2003)).

As described above, identification of particular genes involved in prostate cancer has been challenging. One gene that has been implicated is RNASEL, which encodes a widely expressed latent endoribonuclease that participates in an interferon-inducible RNA-decay pathway believed to degrade viral and cellular RNA, and has been linked to the HPC locus (Carpten, J. et al., *Nat. Genet.* 30:181-84 (2002); Casey, G. et al., *Nat. Genet.* 32(4):581-83 (2002)). Mutations in RNASEL have been associated with increased susceptibility to prostate cancer. For example, in one family, four brothers with prostate cancer carried a disabling mutation in RNASEL, while in another family, four of six brothers with prostate cancer carried a base substitution affecting the initiator methionine codon of RNASEL. Other studies have revealed mutant RNASEL alleles associated with an increased risk of prostate cancer in Finnish men with familial prostate cancer and an Ashkenazi Jewish population (Rokman, A. et al., *Am J. Hum. Genet.* 70:1299-1304 (2002); Rennert, H. et al., *Am J. Hum. Genet.* 71:981-84 (2002)). In addition, the Ser217Leu genotype has been proposed to account for approximately 9% of all sporadic cases in Caucasian Americans younger than 65 years (Stanford, J. L., *Cancer Epidemiol. Biomarkers Prev.* 12(9):876-81 (2003)). In contrast to these positive reports, however, some studies have failed to detect any association between RNASEL alleles with inactivating mutations and prostate cancer (Wang, L. et al., *Am. J. Hum. Genet.* 71:116-23 (2002); Wiklund, F. et al., *Clin. Cancer Res.* 10(21):7150-56 (2004); Maier, C. et. al., *Br. J. Cancer* 92(6):1159-64 (2005)).

The macrophage-scavenger receptor 1 (MSR1) gene, which is located at 8p22, has also been identified as a candidate prostate cancer-susceptibility gene (Xu, J. et al., *Nat. Genet.* 32:321-25 (2002)). A mutant MSR1 allele was detected in approximately 3% of men with nonhereditary prostate cancer but only 0.4% of unaffected men. However, not all subsequent reports have confirmed these initial findings (see, e.g., Lindmark, F. et al., *Prostate* 59(2):132-40 (2004); Seppala, E. H. et al., *Clin. Cancer Res.* 9(14):5252-56 (2003); Wang, L. et al., *Nat. Genet.* 35(2):128-29 (2003); Miller, D. C. et al., *Cancer Res.* 63(13):3486-89 (2003)). MSR1 encodes subunits of a macrophage-scavenger receptor that is capable of binding a variety of ligands, including bacterial lipopolysaccharide and lipoteicholic acid, and oxidized high-density lipoprotein and low-density lipoprotein in serum (Nelson, W. G. et al., *N. Engl. J. Med.* 349(4):366-81 (2003)).

The ELAC2 gene on Chr17p was the first prostate cancer susceptibility gene to be cloned in high risk prostate cancer families from Utah (Tavtigian, S. V., et al., *Nat. Genet.* 27(2):172-80 (2001)). A frameshift mutation (1641InsG) was found in one pedigree. Three additional missense changes: Ser217Leu; Ala541Thr; and Arg781His, were also found to associate with an increased risk of prostate cancer. The relative risk of prostate cancer in men carrying both Ser217Leu and Ala541Thr was found to be 2.37 in a cohort not selected on the basis of family history of prostate cancer (Rebbeck, T. R., et al., *Am. J. Hum. Genet.* 67(4):1014-19 (2000)). Another study described a new termination mutation (Glu216X) in one high incidence prostate cancer family (Wang, L., et al., *Cancer Res.* 61(17):6494-99 (2001)). Other reports have not demonstrated strong association with the three missense mutations, and a recent metaanalysis suggests that the familial risk associated with these mutations is more moderate than was indicated in initial reports (Vesprini, D., et al., *Am. J. Hum. Genet.* 68(4):912-17 (2001); Shea, P. R., et al., *Hum. Genet.* 111(4-5):398-400 (2002); Suarez, B. K, et al., *Cancer Res.* 61(13):4982-84 (2001); Severi, G., et al., *J. Natl. Cancer Inst.* 95(11):818-24 (2003); Fujiwara, H., et al., *J. Hum. Genet.* 47(12):641-48 (2002); Camp, N. J., et al., *Am. J. Hum. Genet.* 71(6):1475-78 (2002)).

Polymorphic variants of genes involved in androgen action (e.g., the androgen receptor (AR) gene, the cytochrome P-450c17 (CYP17) gene, and the steroid-5-α-reductase type II (SRD5A2) gene), have also been implicated in increased risk of prostate cancer (Nelson, W. G. et al., *N. Engl. J. Med.* 349(4):366-81 (2003)). With respect to AR, which encodes the androgen receptor, several genetic epidemiological studies have shown a correlation between an increased risk of prostate cancer and the presence of short androgen-receptor polyglutamine repeats, while other studies have failed to detect such a correlation. Linkage data has also implicated an allelic form of CYP17, an enzyme that catalyzes key reactions in sex-steroid biosynthesis, with prostate cancer (Chang, B. et al., *Int. J. Cancer* 95:354-59 (2001)). Allelic variants of SRD5A2, which encodes the predominant isozyme of 5-α-reductase in the prostate and functions to convert testosterone to the more potent dihydrotestosterone, have been associated with an increased risk of prostate cancer and with a poor prognosis for men with prostate cancer (Makridakis, N. M. et al., *Lancet* 354:975-78 (1999); Nam, R. K. et al., *Urology* 57:199-204 (2001)).

In short, despite the effort of many groups around the world, the genes that account for a substantial fraction of prostate cancer risk have not been identified. Although twin studies have implied that genetic factors are likely to be prominent in prostate cancer, only a handful of genes have been identified as being associated with an increased risk for prostate cancer, and these genes account for only a low percentage of cases. Thus, it is clear that the majority of genetic risk factors for prostate cancer remain to be found. It is likely that these genetic risk factors will include a relatively high number of low-to-medium risk genetic variants. These low-to-medium risk genetic variants may, however, be responsible for a substantial fraction of prostate cancer, and their identification, therefore, a great benefit for public health. Furthermore, none of the published prostate cancer genes have been reported to predict a greater risk for aggressive prostate cancer than for less aggressive prostate cancer.

Extensive genealogical information for a population containing cancer patients has in a recent study been combined

with powerful gene sharing methods to map a locus on chromosome 8q24.21, which has been demonstrated to play a major role in cancer. Various cancer patients and their relatives were genotyped with a genome-wide marker set including 1100 microsatellite markers, with an average marker density of 3-4 cM. (Amundadottir L. T., *Nature Genet.* 38(6): 652-658 (2006)). Association was detected to a single LD block within the locus between positions 128.414 and 128.506 Mb (NCBI build 34) in Utah CEPH HapMap samples.

Colorectal Cancer (CRC) is one of the most commonly diagnosed cancers and one of the leading causes of cancer mortality (Parkin D M, et. al. *CA Cancer J Clin,* 55:74-108 (2005)). Cancers of the colon and rectum accounted for about 1 million new cases in 2002 (9.4% of cancer cases worldwide) and it affects men and women almost equally. The average lifetime risk for an individual in the US to develop CRC is 6% (Jemal A, et al. CA Cancer J Clin., 56:106-30 (2006)). The prognosis is strongly associated with the stage of the disease at diagnosis; therefore, CRC screening presents an opportunity for early cancer detection and cancer prevention.

Colorectal cancer is a consequence of environmental exposures acting upon a background of genetically determined susceptibility. Studies indicate that 30-35% of colorectal cancer risk could be explained by genetic factors (Lichtenstein P, et. al. *N Engl J Med,* 343:78-85 (2000);) Peto J and Mack T M. *Nat Genet,* 26:411-4 (2000); Risch N. *Cancer Epidemiol Biomarkers Prev,* 10:733-41 (2001)). The analysis of cancer occurrence in relatives of cancer patients also lends strong evidence for genetic factors that increase the risk of cancer.

At present only a small percentage of the heritable risk of CRC is identified, usually through the investigation of rare cancer syndromes. High-penetrance mutations in several genes have been identified in rare hereditary colorectal cancer syndromes. The most common of these are the familial adenomatous polyposis (FAP) syndrome and hereditary non-polyposis colorectal cancer (HNPCC) or Lynch syndrome (LS). FAP, caused by mutations in the APC gene, is an autosomal dominant syndrome, characterized by early onset of multiple adenomatous polyps in the colon that eventually progress to cancer. LS is caused by mutations in DNA mismatch repair (MMR) genes and is considered to be the most common hereditary CRC syndrome, comprising approximately 3-5% of all CRCs (de la Chapelle, A. *Fam Cancer,* 4:233-7 (2005)).

The search for additional highly-penetrant CRC genes has not been fruitful and accumulating evidence supports the notion that no single susceptibility gene is likely to explain a large proportion of highly familial or early onset CRC. This has led to the currently favored hypothesis that most of the inherited CRC risk is due to multiple, low genetic risk variants. Each such variant would be expected to carry a small increase in risk; however, if the variant is common, it may contribute significantly to the population attributable risk (PAR).

SUMMARY OF THE INVENTION

The present invention relates to the use of polymorphic markers in diagnostic methods, kits and apparatus for determining susceptibility to prostate cancer and colorectal cancer.

In one aspect, the present invention relates to a method for determining a susceptibility to a cancer selected from prostate cancer and colorectal cancer in a human individual, comprising determining the presence or absence of at least one allele of at least one polymorphic marker in a nucleic acid sample obtained from the individual, or in a genotype dataset from the individual, wherein the at least one polymorphic marker is selected from markers selected from the group consisting of markers within LD Block C11 and LD Block C06, and wherein the presence of the at least one allele is indicative of a susceptibility to the cancer.

In another aspect, the present invention relates to a method for determining a susceptibility to a cancer selected from prostate cancer and colorectal cancer in a human individual, comprising determining the presence or absence of at least one allele of at least one polymorphic marker in a nucleic acid sample obtained from the individual, or in a genotype dataset from the individual, wherein the at least one polymorphic marker is selected from the group consisting of the markers set forth in Table 5 and Table 6, and markers in linkage disequilibirium therewith, and wherein the presence of the at least one allele is indicative of a susceptibility to the cancer. Determining a susceptibility comprises in one embodiment a diagnosis of a susceptibility. Diagnosis may be made by a medical professional, or other professional that provides information about disease risk. Alternatively, diagnosis of a susceptibility is provided by a genotype provider, or by an individual or organization that interprets genotype data for an individual or groups of individuals.

The genotype dataset comprises in one embodiment information about marker identity and the allelic status of the individual for at least one allele of a marker, i.e. information about the identity of at least one allele of the marker in the individual. The genotype dataset may comprise allelic information (information about allelic status) about one or more marker, including two or more markers, three or more markers, five or more markers, ten or more markers, one hundred or more markers, an so on. In some embodiments, the genotype dataset comprises genotype information from a whole-genome assessment of the individual, that may include hundreds of thousands of markers, or even one million or more markers spanning the entire genome of the individual.

Another aspect relates to a method of determining a susceptibility to a cancer selected from prostate cancer and colorectal cancer in a human individual, comprising determining whether at least one at-risk allele in at least one polymorphic marker is present in a genotype dataset derived from the individual, wherein the at least one polymorphic marker is selected from the group consisting of the markers set forth in Tables 5 and 6, and markers in linkage disequilibrium therewith, and wherein determination of the presence of the at least one at-risk allele is indicative of increased susceptibility to cancer.

Another aspect of the invention relates to a method of determining a susceptibility to prostate cancer, the method comprising: obtaining nucleic acid sequence data about a human individual identifying at least one allele of at least one polymorphic marker, wherein different alleles of the at least one polymorphic marker are associated with different susceptibilities to prostate cancer in humans, and determining a susceptibility to prostate cancer from the nucleic acid sequence data, wherein the at least one polymorphic marker is selected from the group consisting of rs10896450, and markers in linkage disequilibirium therewith.

In general, polymorphic genetic markers lead to alternate sequences at the nucleic acid level. If the nucleic acid marker changes the codon of a polypeptide encoded by the nucleic acid, then the marker will also result in alternate sequence at the amino acid level of the encoded polypeptide (polypeptide markers). Determination of the identity of particular alleles at polymorphic markers in a nucleic acid or particular alleles at polypeptide markers comprises whether particular alleles are present at a certain position in the sequence. Sequence data

identifying a particular allele at a marker comprises sufficient sequence to detect the particular allele. For single nucleotide polymorphisms (SNPs) or amino acid polymorphisms described herein, sequence data can comprise sequence at a single position, i.e. the identity of a nucleotide or amino acid at a single position within a sequence. The sequence data can optionally include information about sequence flanking the polymorphic site, which in the case of SNPs spans a single nucleotide.

In certain embodiments, it may be useful to determine the nucleic acid sequence for at least two polymorphic markers. In other embodiments, the nucleic acid sequence for at least three, at least four or at least five or more polymorphic markers is determined. Haplotype information can be derived from an analysis of two or more polymorphic markers. Thus, in certain embodiments, a further step is performed, whereby haplotype information is derived based on sequence data for at least two polymorphic markers.

The invention also provides a method of determining a susceptibility to a cancer selected from prostate cancer and colorectal cancer in a human individual, the method comprising obtaining nucleic acid sequence data about a human individual identifying both alleles of at least two polymorphic markers selected from the markers listed in Table 3 and Table 4, and markers in linkage disequilibrium therewith, determine the identity of at least one haplotype based on the sequence data, and determine a susceptibility to the cancer from the haplotype data.

In certain embodiments, determination of a susceptibility comprises comparing the nucleic acid sequence data to a database containing correlation data between the at least one polymorphic marker and susceptibility to cancer. In some embodiments, the database comprises at least one risk measure of susceptibility to cancer for the at least one marker. The sequence database can for example be provided as a look-up table that contains data that indicates the susceptibility of cancer for any one, or a plurality of, particular polymorphisms. The database may also contain data that indicates the susceptibility for a particular haplotype that comprises at least two polymorphic markers.

Obtaining nucleic acid sequence data can in certain embodiments comprise obtaining a biological sample from the human individual and analyzing sequence of the at least one polymorphic marker in nucleic acid in the sample. Analyzing sequence can comprise determining the presence or absence of at least one allele of the at least one polymorphic marker. Determination of the presence of a particular susceptibility allele (e.g., an at-risk allele) is indicative of susceptibility to cancer in the human individual. Determination of the absence of a particular susceptibility allele is indicative that the particular susceptibility due to the at least one polymorphism is not present in the individual.

In some embodiments, obtaining nucleic acid sequence data comprises obtaining nucleic acid sequence information from a preexisting record. The preexisting record can for example be a computer file or database containing sequence data, such as genotype data, for the human individual, for at least one polymorphic marker.

Susceptibility determined by the diagnostic methods of the invention can be reported to a particular entity. In some embodiments, the at least one entity is selected from the group consisting of the individual, a guardian of the individual, a genetic service provider, a physician, a medical organization, and a medical insurer.

In certain embodiments, genetic markers associated with risk of prostate cancer and/or colorectal cancer as described herein are indicative of different response rates to particular treatment modalities for the cancer. Thus, in certain embodiments, the presence of the marker or haplotype is indicative of a different response rate of the subject to a particular treatment modality.

Another aspect of the invention relates to a method of identification of a marker for use in assessing susceptibility to prostate cancer, the method comprising

identifying at least one polymorphic marker within LD Block C06 or LD Block C11, or at least one polymorphic marker in linkage disequilibrium therewith;

determining the genotype status of a sample of individuals diagnosed with, or having a susceptibility to, prostate cancer; and

determining the genotype status of a sample of control individuals;

wherein a significant difference in frequency of at least one allele in at least one polymorphism in individuals diagnosed with, or having a susceptibility to, prostate cancer, as compared with the frequency of the at least one allele in the control sample is indicative of the at least one polymorphism being useful for assessing susceptibility to prostate cancer.

The invention also relates, in another aspect, to a method of identification of a marker for use in assessing susceptibility to colorectal cancer, the method comprising

identifying at least one polymorphic marker within The LD Block C11 genomic region, or at least one polymorphic marker in linkage disequilibrium therewith;

determining the genotype status of a sample of individuals diagnosed with, or having a susceptibility to, colorectal cancer; and

determining the genotype status of a sample of control individuals;

wherein a significant difference in frequency of at least one allele in at least one polymorphism in individuals diagnosed with, or having a susceptibility to, colorectal cancer, as compared with the frequency of the at least one allele in the control sample is indicative of the at least one polymorphism being useful for assessing susceptibility to colorectal cancer. In one embodiment, an increase in frequency of the at least one allele in the at least one polymorphism in individuals diagnosed with, or having a susceptibility to, the cancer, as compared with the frequency of the at least one allele in the control sample is indicative of the at least one polymorphism being useful for assessing increased susceptibility to the cancer. In another embodiment, a decrease in frequency of the at least one allele in the at least one polymorphism in individuals diagnosed with, or having a susceptibility to, the cancer, as compared with the frequency of the at least one allele in the control sample is indicative of the at least one polymorphism being useful for assessing decreased susceptibility to, or protection against, the cancer.

The invention, in another aspect, also relates to a method of genotyping a nucleic acid sample obtained from a human individual at risk for, or diagnosed with, a cancer selected from prostate cancer and colorectal cancer, comprising determining the presence or absence of at least one allele of at least one polymorphic marker in the sample, wherein the at least one marker is selected from the markers set forth in Table 3 and Table 4, and markers in linkage disequilibrium therewith, and wherein the presence of the at least one allele is indicative of a susceptibility to the cancer. In one embodiment, genotyping comprises amplifying a segment of a nucleic acid that comprises the at least one polymorphic marker by Polymerase Chain Reaction (PCR), using a nucleotide primer pair flanking the at least one polymorphic marker. In another embodiment, genotyping is performed using a process selected from allele-specific probe hybridization, allele-spe-

cific primer extension, allele-specific amplification, nucleic acid sequencing, 5'-exonuclease digestion, molecular beacon assay, oligonucleotide ligation assay, size analysis, and single-stranded conformation analysis. In one preferred embodiment, the process comprises allele-specific probe hybridization. In another preferred embodiment, the process comprises DNA sequencing. In yet another preferred embodiment, genotyping comprises the steps of

contacting copies of the nucleic acid with a detection oligonucleotide probe and an enhancer oligonucleotide probe under conditions for specific hybridization of the oligonucleotide probe with the nucleic acid;

wherein

the detection oligonucleotide probe is from 5-100 nucleotides in length and specifically hybridizes to a first segment of the nucleic acid whose nucleotide sequence is given by SEQ ID NO:2 that comprises at least one polymorphic site;

the detection oligonucleotide probe comprises a detectable label at its 3' terminus and a quenching moiety at its 5' terminus;

the enhancer oligonucleotide is from 5-100 nucleotides in length and is complementary to a second segment of the nucleotide sequence that is 5' relative to the oligonucleotide probe, such that the enhancer oligonucleotide is located 3' relative to the detection oligonucleotide probe when both oligonucleotides are hybridized to the nucleic acid; and

a single base gap exists between the first segment and the second segment, such that when the oligonucleotide probe and the enhancer oligonucleotide probe are both hybridized to the nucleic acid, a single base gap exists between the oligonucleotides;

treating the nucleic acid with an endonuclease that will cleave the detectable label from the 3' terminus of the detection probe to release free detectable label when the detection probe is hybridized to the nucleic acid; and

measuring free detectable label, wherein the presence of the free detectable label indicates that the detection probe specifically hybridizes to the first segment of the nucleic acid, and indicates the sequence of the polymorphic site as the complement of the detection probe. The copies of the nucleic acid are preferably provided by amplification by Polymerase Chain Reaction (PCR).

Another aspect relates to a method of assessing an individual for probability of response to a therapeutic agent for preventing and/or ameliorating symptoms associated with cancer, comprising: determining the presence or absence of at least one allele of at least one polymorphic marker in a nucleic acid sample obtained from the individual, wherein the at least one polymorphic marker is selected from the group consisting of the polymorphic markers set forth in Table 3 and Table 4, and markers in linkage disequilibrium therewith, wherein the presence of the at least one allele of the at least one marker is indicative of a probability of a positive response to a cancer therapeutic agent.

Another aspect relates to a method of predicting prognosis of an individual diagnosed with a cancer selected from prostate cancer and colorectal cancer, the method comprising determining the presence or absence of at least one allele of at least one polymorphic marker in a nucleic acid sample obtained from the individual, wherein the at least one polymorphic marker is selected from the group consisting of the polymorphic markers listed in Table 3 and Table 4, and markers in linkage disequilibrium therewith, wherein the presence of the at least one allele is indicative of a worse prognosis of the cancer in the individual.

Yet another aspect relates to a method of monitoring progress of a treatment of an individual undergoing treatment for a cancer selected from prostate cancer and colorectal cancer, the method comprising determining the presence or absence of at least one allele of at least one polymorphic marker in a nucleic acid sample obtained from the individual, wherein the at least one polymorphic marker is selected from the group consisting of the polymorphic markers listed in Table 3 and Table 4, and markers in linkage disequilibrium therewith, wherein the presence of the at least one allele is indicative of the treatment outcome of the individual.

The invention in another aspect relates to a kit for assessing susceptibility to a cancer selected from prostate cancer and colorectal cancer in a human individual, the kit comprising reagents for selectively detecting at least one allele of at least one polymorphic marker in the genome of the individual, wherein the polymorphic marker is selected from the group consisting of the polymorphic markers set forth in Table 5 and Table 6, and markers in linkage disequilibrium therewith, and a collection of data comprising correlation data between the polymorphic markers assessed by the kit and susceptibility to prostate cancer and/or colorectal cancer. In one embodiment, the reagents comprise at least one contiguous oligonucleotide that hybridizes to a fragment of the genome of the individual comprising the at least one polymorphic marker, a buffer and a detectable label. In another embodiment, the reagents comprise at least one pair of oligonucleotides that hybridize to opposite strands of a genomic nucleic acid segment obtained from the subject, wherein each oligonucleotide primer pair is designed to selectively amplify a fragment of the genome of the individual that includes one polymorphic marker, and wherein the fragment is at least 30 base pairs in size. In yet another embodiment, the at least one oligonucleotide is completely complementary to the genome of the individual. In one embodiment, the oligonucleotide is about 18 to about 50 nucleotides in length. In another embodiment, the oligonucleotide is 20-30 nucleotides in length.

In one preferred embodiment, the kit comprises:

a detection oligonucleotide probe that is from 5-100 nucleotides in length;

an enhancer oligonucleotide probe that is from 5-100 nucleotides in length; and

an endonuclease enzyme;

wherein the detection oligonucleotide probe specifically hybridizes to a first segment of the nucleic acid whose nucleotide sequence is given by SEQ ID NO: 201 that comprises at least one polymorphic site; and

wherein the detection oligonucleotide probe comprises a detectable label at its 3' terminus and a quenching moiety at its 5' terminus;

wherein the enhancer oligonucleotide is from 5-100 nucleotides in length and is complementary to a second segment of the nucleotide sequence that is 5' relative to the oligonucleotide probe, such that the enhancer oligonucleotide is located 3' relative to the detection oligonucleotide probe when both oligonucleotides are hybridized to the nucleic acid;

wherein a single base gap exists between the first segment and the second segment, such that when the oligonucleotide probe and the enhancer oligonucleotide probe are both hybridized to the nucleic acid, a single base gap exists between the oligonucleotides; and

wherein treating the nucleic acid with the endonuclease will cleave the detectable label from the 3' terminus of the detection probe to release free detectable label when the detection probe is hybridized to the nucleic acid.

Another aspect of the invention relates to the use of an oligonucleotide probe in the manufacture of a diagnostic reagent for diagnosing and/or assessing susceptibility to a cancer selected from prostate cancer and colorectal cancer in

a human individual, wherein the probe hybridizes to a segment of a nucleic acid within LD Block C06 or LD Block C11 that comprises at least one polymorphic site, wherein the fragment is 15-500 nucleotides in length.

The invention also provides computer-implemented aspects. In one such aspect, the invention provides a computer-readable medium having computer executable instructions for determining susceptibility to a cancer selected from prostate cancer and colorectal cancer in an individual, the computer readable medium comprising:

data representing at least one polymorphic marker; and a routine stored on the computer readable medium and adapted to be executed by a processor to determine susceptibility to the cancer in an individual based on the allelic status of at least one allele of said at least one polymorphic marker in the individual.

In one embodiment, said data representing at least one polymorphic marker comprises at least one parameter indicative of the susceptibility to the cancer linked to said at least one polymorphic marker. In another embodiment, said data representing at least one polymorphic marker comprises data indicative of the allelic status of at least one allele of said at least one allelic marker in said individual. In another embodiment, said routine is adapted to receive input data indicative of the allelic status for at least one allele of said at least one allelic marker in said individual. In a preferred embodiment, the at least one marker is selected from rs10896450 and rs10943605, and markers in linkage disequilibrium therewith. In another preferred embodiment, the at least one polymorphic marker is selected from the markers set forth in Table 3 and Table 4.

The invention further provides an apparatus for determining a genetic indicator for a cancer selected from prostate cancer and colorectal cancer in a human individual, comprising:

a processor,

a computer readable memory having computer executable instructions adapted to be executed on the processor to analyze marker and/or haplotype information for at least one human individual with respect to a cancer selected from prostate cancer and colorectal cancer, and

generate an output based on the marker or haplotype information, wherein the output comprises a risk measure of the at least one marker or haplotype as a genetic indicator of the cancer for the human individual.

In one embodiment, the computer readable memory comprises data indicative of the frequency of at least one allele of at least one polymorphic marker or at least one haplotype in a plurality of individuals diagnosed with prostate cancer and/or colorectal cancer, and data indicative of the frequency of at the least one allele of at least one polymorphic marker or at least one haplotype in a plurality of reference individuals, and wherein a risk measure is based on a comparison of the at least one marker and/or haplotype status for the human individual to the data indicative of the frequency of the at least one marker and/or haplotype information for the plurality of individuals diagnosed with the cancer. In one embodiment, the computer readable memory further comprises data indicative of a risk of developing prostate cancer and/or colorectal cancer associated with at least one allele of at least one polymorphic marker or at least one haplotype, and wherein a risk measure for the human individual is based on a comparison of the at least one marker and/or haplotype status for the human individual to the risk associated with the at least one allele of the at least one polymorphic marker or the at least one haplotype. In another embodiment, the computer readable memory further comprises data indicative of the frequency of at least one allele of at least one polymorphic marker or at least one haplotype in a plurality of individuals diagnosed with a cancer selected from prostate cancer and colorectal cancer, and data indicative of the frequency of at the least one allele of at least one polymorphic marker or at least one haplotype in a plurality of reference individuals, and wherein risk of developing the cancer is based on a comparison of the frequency of the at least one allele or haplotype in individuals diagnosed with the cancer, and reference individuals. In a preferred embodiment, the at least one marker is selected from rs10943605 and rs10896450, and markers in linkage disequilibrium therewith. In another preferred embodiment, the at least one polymorphic marker is selected from the markers set forth in Table 3 and Table 4.

Different embodiments of the various aspects of the invention relate to specific use of the polymorphic variants described herein to be associated with prostate cancer and colorectal cancer, or variants (polymorphic markers) in linkage disequilibrium therewith. In one embodiment of the invention, the at least one marker is selected from the markers within LD Block C06 and/or LD Block C11, as defined herein, and markers in linkage disequilibrium therewith. In one such embodiment, the at least one marker is selected from markers within LD Block C06 and/or LD Block C11. In one embodiment, the at least one polymorphic marker is selected from the markers set forth in Table 5 and Table 6. In another embodiment, the at least one polymorphic marker comprises at least one marker selected from the group of markers set forth in Table 3 and Table 4, and markers in linkage disequilibrium therewith. One embodiment relates to at least one marker selected from the group consisting of marker rs10896450, marker rs11228565, marker rs7947353 and marker rs10943605, and markers in linkage disequilibrium therewith. One embodiment relates to marker rs10896450, and markers in linkage disequilibrium therewith. One embodiment relates to marker rs11228565, and markers in linkage disequilibrium therewith. One embodiment relates to marker rs10943605, and markers in linkage disequilibrium therewith. One embodiment relates to marker rs10896450. Another embodiment relates to marker rs11228565. Another embodiment relates to marker rs10943605. In certain embodiments, the cancer assessed by the invention is prostate cancer. In certain other embodiments, the cancer is colorectal cancer. In one such embodiment, the at least one polymorphic marker is selected from the group of markers set forth in Table 3. In another embodiment, the marker is rs10943605, and markers in linkage disequilibrium therewith.

Some embodiments of the invention, further comprise assessing the frequency of at least one haplotype in the individual.

The methods of the invention comprise, in some embodiments, an additional step of assessing at least one biomarker in a sample from the individual. The sample can be a blood sample or a cancer biopsy sample, or any other biological sample derived from an individual that is suitable for assessing the presence or absence, or for quantitative determination, of at least one biomarker. The biomarker is preferably a biological molecule that represents directly or indirectly the disease state in question, i.e. prostate cancer or colorectal cancer. An exemplary biomarker is PSA. Other embodiments of the methods of the invention further comprise analyzing non-genetic information to make risk assessment, diagnosis, or prognosis of the individual. The non-genetic information is in some embodiments selected from age, gender, ethnicity, socioeconomic status, previous disease diagnosis, medical history of subject, family history of cancer, biochemical measurements, and clinical measurements.

Other genetic risk factors for cancer, e.g., prostate cancer and/or colorectal cancer, can be assessed in combination with the markers of the present invention found to be predictive of these cancers, for providing overall risk assessment of prostate cancer and/or colorectal cancer. Thus, in one embodiment, the methods of the invention relate to further steps comprising assessing the presence of absence of at least one additional genetic risk factor for prostate cancer or colorectal cancer in the individual. In certain embodiments, the additional genetic risk factor is not associated, defined by values of r^2 of at least 0.2 and/or values of |D'| of at least 0.8, to markers set forth in Tables 3 and 4, in particular marker rs10896450, marker rs11228565, marker rs7947353 and marker rs10943605. Such additional risk factor are in certain embodiments risk factors for a particular type of cancer, i.e. cancer at a particular site (e.g., prostate cancer and/or colorectal cancer). In certain other embodiments, such additional risk factors are susceptibility variants for multiple forms of cancer.

Thus, in certain embodiments, a further step is included, comprising determining whether at least one at-risk allele of at least one at-risk variant for a cancer selected from prostate cancer and colorectal cancer not in linkage disequilibrium with any one of the markers rs10896450, rs11228565, rs7947353 and rs10943605 are present in a sample comprising genomic DNA from a human individual or a genotype dataset derived from a human individual. In other words, genetic markers in other locations in the genome can be useful in combination with the markers of the present invention, so as to determine overall risk of the cancer based on multiple genetic variants. In one embodiment, the at least one at-risk variant for cancer is not in linkage disequilibrium with marker rs10896450. Selection of markers that are not in linkage disequilibrium (not in LD) can be based on a suitable measure for linkage disequilibrium, as described further herein. In certain embodiments, markers that are not in linkage disequilibrium have values for the LD measure r^2 correlating the markers of less than 0.2. In certain other embodiments, markers that are not in LD have values for r^2 correlating the markers of less than 0.15, including less than 0.10, less than 0.05, less than 0.02 and less than 0.01. Other suitable numerical values for establishing that markers are not in LD are contemplated, including values bridging any of the above-mentioned values.

The risk factors are in one embodiment selected from rs1447295, rs4430796, rs1859962, rs5945572, rs6983267, rs16901979 and rs10505483, and markers in linkage disequilibrium therewith. In another embodiment, the additional genetic risk factor is selected from the group consisting of rs2710646 allele A, rs16901979 allele A, rs1447295 allele A, rs6983267 allele G, rs10896450 allele G, rs1859962 allele G, rs4430796 allele A and rs5945572 allele A. In other embodiments, the additional genetic risk factor is selected from markers in linkage disequilibrium with any of the markers rs2710646, rs16901979, rs1447295, rs6983267, rs10896450, rs1859962, rs4430796 and rs5945572. An overall risk for prostate cancer and/or colon cancer is in one embodiment calculated based on the genotype status of the individual.

In certain embodiments, the susceptibility is increased susceptibility. Increased susceptibility is in certain embodiments accompanied by an odds ratio (OR) or relative risk (RR) of at least 1.10. In other embodiments, the odds ratio or relative risk is at least 1.15. In other embodiments, the relative risk or odds ratio is at least 1.20. In one embodiment, the at least one marker or haplotype comprises marker rs10896450 allele G, marker rs7947353 allele A and marker rs10943605 allele G.

In certain other embodiments, the susceptibility is decreased susceptibility. The decreased susceptibility is in some embodiments accompanied by a relative risk or odds ratio of less than 0.9.

Certain embodiments of the invention relate to aggressive forms of prostate cancer. In some embodiments, the prostate cancer is an aggressive prostate cancer as defined by a combined Gleason score of 7(4+3)–10. In other embodiments, the prostate cancer is a less aggressive prostate cancer as defined by a combined Gleason score of 2-7(3+4).

In certain embodiments of the invention, the individual is of a specific ancestry. One embodiment relates to the ancestry being Caucasian ancestry. In other embodiments, the ancestry is African ancestry or African American ancestry. In another embodiment, the ancestry is European ancestry. The ancestry is in some embodiment self-reported. In other embodiments, the ancestry is determined by detecting at least one allele of at least one polymorphic marker in a sample from the individual, wherein the presence or absence of the allele is indicative of the ancestry of the individual.

In certain embodiments of the invention, linkage disequilibrium is determined using the linkage disequilibrium measures r^2 and |D'|, which give a quantitative measure of the extent of linkage disequilibrium (LD) between two genetic element (e.g., polymorphic markers). Certain numerical values of these measures for particular markers are indicative of the markers being in linkage disequilibrium, as described further herein. The higher the numerical value for the LD measures r^2 and |D'|, the stronger the LD between the genetic elements is, as further described herein. In one embodiment of the invention, linkage disequilibrium between marker (i.e., LD values indicative of the markers being in linkage disequilibrium) is defined as $r^2>0.1$. In another embodiment, linkage disequilibrium is defined as $r^2>0.2$. Other embodiments can include other definitions of linkage disequilibrium, such as $r^2>0.25$, $r^2>0.3$, $r^2>0.35$, $r^2>0.4$, $r^2>0.45$, $r^2>0.5$, $r^2>0.55$, $r^2>0.6$, $r^2>0.65$, $r^2>0.7$, $r^2>0.75$, $r^2>0.8$, $r^2>0.85$, $r^2>0.9$, $r^2>0.95$, $r^2>0.96$, $r^2>0.97$, $r^2>0.98$, or $r^2>0.99$. Linkage disequilibrium can in certain embodiments also be defined as |D'|>0.2, or as |D'|>0.3, |D'|>0.4, |D'|>0.5, |D'|>0.6, |D'|>0.7, |D'|>0.8, |D'|>0.9, |D'|>0.95, |D'|>0.98 or |D'|>0.99. In certain embodiments, linkage disequilibrium is defined as fulfilling two criteria of r^2 and |D'|, such as $r^2>0.2$ and/or |D'|>0.8. Other combinations of values for r^2 and |D'| are also possible and within scope of the present invention, including but not limited to the values for these parameters set forth in the above.

It should be understood that all combinations of features described herein are contemplated, even if the combination of feature is not specifically found in the same sentence or paragraph herein. This includes, but is not limited to, the use of all markers disclosed herein, alone or in combination, for analysis individually or in haplotypes, in all aspects of the invention as described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other objects, features and advantages of the invention will be apparent from the following more particular description of preferred embodiments of the invention.

The FIGURE provides a diagram illustrating a computer-implemented system utilizing risk variants as described herein.

DETAILED DESCRIPTION OF THE INVENTION

The present invention discloses polymorphic variants and haplotypes that have been found to be associated with pros-

tate and colorectal cancer. Such markers and haplotypes are useful for diagnostic purposes, as described in further detail herein.

Definitions

Unless otherwise indicated, nucleic acid sequences are written left to right in a 5' to 3' orientation. Numeric ranges recited within the specification are inclusive of the numbers defining the range and include each integer or any non-integer fraction within the defined range. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by the ordinary person skilled in the art to which the invention pertains.

The following terms shall, in the present context, have the meaning as indicated:

A "polymorphic marker", sometimes referred to as a "marker", as described herein, refers to a genomic polymorphic site. Each polymorphic marker has at least two sequence variations characteristic of particular alleles at the polymorphic site. Thus, genetic association to a polymorphic marker implies that there is association to at least one specific allele of that particular polymorphic marker. The marker can comprise any allele of any variant type found in the genome, including SNPs, mini- or microsatellites, translocations and copy number variations (insertions, deletions, duplications). Polymorphic markers can be of any measurable frequency in the population. For mapping of disease genes, polymorphic markers with population frequency higher than 5-10% are in general most useful. However, polymorphic markers may also have lower population frequencies, such as 1-5% frequency, or even lower frequency, in particular copy number variations (CNVs). The term shall, in the present context, be taken to include polymorphic markers with any population frequency.

An "allele" refers to the nucleotide sequence of a given locus (position) on a chromosome. A polymorphic marker allele thus refers to the composition (i.e., sequence) of the marker on a chromosome. Genomic DNA from an individual contains two alleles for any given polymorphic marker, representative of each copy of the marker on each chromosome. Sequence codes for nucleotides used herein are: A=1, C=2, G=3, T=4. For microsatellite alleles, the CEPH sample (Centre d'Etudes du Polymorphisme Humain, genomics repository, CEPH sample 1347-02) is used as a reference, the shorter allele of each microsatellite in this sample is set as 0 and all other alleles in other samples are numbered in relation to this reference. Thus, e.g., allele 1 is 1 bp longer than the shorter allele in the CEPH sample, allele 2 is 2 bp longer than the shorter allele in the CEPH sample, allele 3 is 3 bp longer than the lower allele in the CEPH sample, etc., and allele −1 is 1 bp shorter than the shorter allele in the CEPH sample, allele −2 is 2 bp shorter than the shorter allele in the CEPH sample, etc.

Sequence conucleotide ambiguity as described herein is as proposed by IUPAC-IUB. These codes are compatible with the codes used by the EMBL, GenBank, and PIR databases.

IUB code	Meaning
A	Adenosine
C	Cytidine
G	Guanine
T	Thymidine
R	G or A
Y	T or C
K	G or T
M	A or C

-continued

IUB code	Meaning
S	G or C
W	A or T
B	C, G or T
D	A, G or T
H	A, C or T
V	A, C or G
N	A, C, G or T (Any base)

A nucleotide position at which more than one sequence is possible in a population (either a natural population or a synthetic population, e.g., a library of synthetic molecules) is referred to herein as a "polymorphic site".

A "Single Nucleotide Polymorphism" or "SNP" is a DNA sequence variation occurring when a single nucleotide at a specific location in the genome differs between members of a species or between paired chromosomes in an individual. Most SNP polymorphisms have two alleles. Each individual is in this instance either homozygous for one allele of the polymorphism (i.e. both chromosomal copies of the individual have the same nucleotide at the SNP location), or the individual is heterozygous (i.e. the two sister chromosomes of the individual contain different nucleotides). The SNP nomenclature as reported herein refers to the official Reference SNP (rs) ID identification tag as assigned to each unique SNP by the National Center for Biotechnological Information (NCBI).

A "variant", as described herein, refers to a segment of DNA that differs from the reference DNA. A "marker" or a "polymorphic marker", as defined herein, is a variant. Alleles that differ from the reference are referred to as "variant" alleles.

A "microsatellite" is a polymorphic marker that has multiple small repeats of bases that are 2-8 nucleotides in length (such as CA repeats) at a particular site, in which the number of repeat lengths varies in the general population.

An "indel" is a common form of polymorphism comprising a small insertion or deletion that is typically only a few nucleotides long.

A "haplotype," as described herein, refers to a segment of genomic DNA within one strand of DNA that is characterized by a specific combination of alleles arranged along the segment. For diploid organisms such as humans, a haplotype comprises one member of the pair of alleles for each polymorphic marker or locus along the segment. In a certain embodiment, the haplotype can comprise two or more alleles, three or more alleles, four or more alleles, or five or more alleles. Haplotypes are described herein in the context of the marker name and the allele of the marker in that haplotype, e.g., "3 rs10896450" refers to the 3 allele of marker rs10896450 being in the haplotype, and is equivalent to "rs10896450 allele 3". Furthermore, allelic codes in haplotypes are as for individual markers, i.e. 1=A, 2=C, 3=G and 4=T.

The term "susceptibility", as described herein, encompasses both increased susceptibility and decreased susceptibility. Thus, particular polymorphic markers and/or haplotypes of the invention may be characteristic of increased susceptibility (i.e., increased risk) of prostate cancer, as characterized by a relative risk (RR) or odds ratio (OR) of greater than one for the particular allele or haplotype. Alternatively, the markers and/or haplotypes of the invention are characteristic of decreased susceptibility (i.e., decreased risk) of prostate cancer, as characterized by a relative risk of less than one.

The term "and/or" shall in the present context be understood to indicate that either or both of the items connected by it are involved. In other words, the term herein shall be taken to mean "one or the other or both".

The term "look-up table", as described herein, is a table that correlates one form of data to another form, or one or more forms of data to a predicted outcome to which the data is relevant, such as phenotype or trait. For example, a look-up table can comprise a correlation between allelic data for at least one polymorphic marker and a particular trait or phenotype, such as a particular disease diagnosis, that an individual who comprises the particular allelic data is likely to display, or is more likely to display than individuals who do not comprise the particular allelic data. Look-up tables can be multidimensional, i.e. they can contain information about multiple alleles for single markers simultaneously, or the can contain information about multiple markers, and they may also comprise other factors, such as particulars about diseases diagnoses, racial information, biomarkers, biochemical measurements, therapeutic methods or drugs, etc.

A "computer-readable medium", is an information storage medium that can be accessed by a computer using a commercially available or custom-made interface. Exemplary compute-readable media include memory (e.g., RAM, ROM, flash memory, etc.), optical storage media (e.g., CD-ROM), magnetic storage media (e.g., computer hard drives, floppy disks, etc.), punch cards, or other commercially available media. Information may be transferred between a system of interest and a medium, between computers, or between computers and the computer-readable medium for storage or access of stored information. Such transmission can be electrical, or by other available methods, such as IR links, wireless connections, etc.

A "nucleic acid sample", as described herein, refer to a sample obtained from an individual that contains nucleic acid (DNA or RNA). In certain embodiments, i.e. the detection of specific polymorphic markers and/or haplotypes, the nucleic acid sample comprises genomic DNA. Such a nucleic acid sample can be obtained from any source that contains genomic DNA, including as a blood sample, sample of amniotic fluid, sample of cerebrospinal fluid, or tissue sample from skin, muscle, buccal or conjunctival mucosa, placenta, gastrointestinal tract or other organs.

The term "prostate cancer therapeutic agent" and "colorectal cancer therapeutic agent", as described herein, refers to an agent that can be used to ameliorate or prevent symptoms associated with prostate cancer and colorectal cancer, respectively.

The term "prostate cancer-associated nucleic acid" and "colorectal cancer-associated nucleic acid", as described herein, refers to a nucleic acid that has been found to be associated to prostate and/or colorectal cancer. This includes, but is not limited to, the markers and haplotypes described herein and markers and haplotypes in strong linkage disequilibrium (LD) therewith. In one embodiment, a prostate and/or colon cancer-associated nucleic acid refers to an LD-block found to be associated with prostate and/or colorectal cancer through at least one polymorphic marker located within the LD block C06 or associated with the LD block C11.

"Aggressive prostate cancer", as described herein, refers to prostate cancer with combined Gleason grades of 7 or higher OR stage T3 or higher OR node positive OR metastasis positive disease OR death because of prostate cancer. Note that it is sufficient to have one of these criteria to be determined aggressive prostate cancer. These clinical parameters are well known surrogates for increased aggressiveness of the disease.

The term "LD block 06", as described herein, refers to the Linkage Disequilibrium (LD) block on Chromosome 6 between positions 79,300,773 and 79,917,888 of NCBI (National Center for Biotechnology Information) Build 36, spanning the region flanked by the SNP markers rs611737 and rs9294130.

The term "LD block C11", as described herein, refers to the Linkage Disequilibrium (LD) block on Chromosome 11 between positions 68,709,630 and 68,782,375 of NCBI (National Center for Biotechnology Information) Build 36, spanning the region flanked by the SNP markers rs7128814 and rs3884627. The LD block C11 has the sequence as set forth in SEQ ID NO:201 herein, based on NCBI Build 36 of the human genome sequence assembly.

A genome-wide search for variants associated with prostate and/or colorectal cancer has identified two genomic regions associated with these cancers. Markers rs10896450 and rs7947353 on Chr 11q13.3, within a region herein called LD Block C11, were identified as contributing to risk of prostate cancer (see Table 1). The two markers are fully correlated (D'=1 and r^2=1; see footnote of Table 1) and do therefore essentially represent the same association signal. The G allele of SNP marker rs10896450 confers increased risk of prostate cancer, with an odds ratio (OR) of 1.17 in the Icelandic samples ($P=6.6\times10^{-5}$). The initial discovery in an Icelandic prostate cancer cohort was validated by analysis of marker rs7947353, which is perfectly correlated (i.e., a perfect surrogate marker) to rs10896450, in prostate cancer cohorts from the Netherlands, Spain and US (Chicago, Ill.). The results for these additional cohorts are comparable to the results for the Icelandic discovery cohort, showing that the initial observation represents a true association signal. Overall, the association is significant with a p-value of 1.43×10^{-6}.

A follow-up analysis revealed that marker rs11228565, located within LD Block C11, shows that this marker associated very significantly with prostate cancer, with an OR of 1.23 for all cohorts and an overall P-value of 6.7×10^{-12} (Table 7).

A second region on Chromosome 6 (LD Block C06) was identified as a prostate cancer susceptibility region, as shown in Table 2a. The association of the G allele of the rs10943605 SNP marker observed in the Icelandic cohort was replicated in Dutch and Spanish cohort, both which gave increased risk conferred by the G allele, although only the replication in the Dutch cohort is statistically significant. Surprisingly, the G allele of the rs10943605 SNP marker was also found to be associated with increased risk of developing colorectal cancer, with an OR of 1.14 in the Icelandic colorectal cancer samples ($P=4.8\times10^{-3}$) (Table 2b).

Accordingly, the present invention provides methods for determining a susceptibility to prostate cancer and colorectal cancer, by assessing for the presence or absence of particular alleles of polymorphic markers within the LD Block C06 and/or LD Block C11 genomic segments that are indicative of risk of prostate cancer and colorectal cancer. Determination of the presence of such marker alleles is indicative of risk of prostate cancer and/or colorectal cancer in the individual.

Assessment for Markers and Haplotypes

The genomic sequence within populations is not identical when individuals are compared. Rather, the genome exhibits sequence variability between individuals at many locations in the genome. Such variations in sequence are commonly referred to as polymorphisms, and there are many such sites within each genome For example, the human genome exhibits sequence variations which occur on average every 500 base pairs. The most common sequence variant consists of base variations at a single base position in the genome, and

such sequence variants, or polymorphisms, are commonly called Single Nucleotide Polymorphisms ("SNPs"). These SNPs are believed to have occurred in a single mutational event, and therefore there are usually two possible alleles possible at each SNP site; the original allele and the mutated allele. Due to natural genetic drift and possibly also selective pressure, the original mutation has resulted in a polymorphism characterized by a particular frequency of its alleles in any given population. Many other types of sequence variants are found in the human genome, including mini- and microsatellites, and insertions, deletions and inversions (also called copy number variations (CNVs)). A polymorphic microsatellite has multiple small repeats of bases (such as CA repeats, TG on the complimentary strand) at a particular site in which the number of repeat lengths varies in the general population. In general terms, each version of the sequence with respect to the polymorphic site represents a specific allele of the polymorphic site. These sequence variants can all be referred to as polymorphisms, occurring at specific polymorphic sites characteristic of the sequence variant in question. In general terms, polymorphisms can comprise any number of specific alleles. Thus in one embodiment of the invention, the polymorphism is characterized by the presence of two or more alleles in any given population. In another embodiment, the polymorphism is characterized by the presence of three or more alleles. In other embodiments, the polymorphism is characterized by four or more alleles, five or more alleles, six or more alleles, seven or more alleles, nine or more alleles, or ten or more alleles. All such polymorphisms can be utilized in the methods and kits of the present invention, and are thus within the scope of the invention.

Due to their abundance, SNPs account for a majority of sequence variation in the human genome. Over 6 million SNPs have been validated to date (ncbi.nlm.nih.gov/projects/SNP/snp_summary.cgi). However, CNVs are receiving increased attention. These large-scale polymorphisms (typically 1 kb or larger) account for polymorphic variation affecting a substantial proportion of the assembled human genome; known CNVs cover over 15% of the human genome sequence (Estivill, X., Armengol; L., *PloS Genetics* 3:1787-99 (2007). A http://projects.tcag.ca/variation/). Most of these polymorphisms are however very rare, and on average affect only a fraction of the genomic sequence of each individual. CNVs are known to affect gene expression, phenotypic variation and adaptation by disrupting gene dosage, and are also known to cause disease (microdeletion and microduplication disorders) and confer risk of common complex diseases, including HIV-1 infection and glomerulonephritis (Redon, R., et al. *Nature* 23:444-454 (2006)). It is thus possible that either previously described or unknown CNVs represent causative variants in linkage disequilibrium with the markers described herein to be associated with prostate and colorectal cancer. Methods for detecting CNVs include comparative genomic hybridization (CGH) and genotyping, including use of genotyping arrays, as described by Carter (*Nature Genetics* 39:S16-S21 (2007)). The Database of Genomic Variants (http://projects.tcag.ca/variation/) contains updated information about the location, type and size of described CNVs. The database currently contains data for over 15,000 CNVs.

In some instances, reference is made to different alleles at a polymorphic site without choosing a reference allele. Alternatively, a reference sequence can be referred to for a particular polymorphic site. The reference allele is sometimes referred to as the "wild-type" allele and it usually is chosen as either the first sequenced allele or as the allele from a "non-affected" individual (e.g., an individual that does not display a trait or disease phenotype).

Alleles for SNP markers as referred to herein refer to the bases A, C, G or T as they occur at the polymorphic site in the SNP assay employed. The allele codes for SNPs used herein are as follows: 1=A, 2=C, 3=G, 4=T. The person skilled in the art will however realise that by assaying or reading the opposite DNA strand, the complementary allele can in each case be measured. Thus, for a polymorphic site (polymorphic marker) characterized by an A/G polymorphism, the assay employed may be designed to specifically detect the presence of one or both of the two bases possible, e.g. A and G. Alternatively, by designing an assay that is designed to detect the complimentary strand on the DNA template, the presence of the complementary bases T and C can be measured. Quantitatively (for example, in terms of risk estimates), identical results would be obtained from measurement of either DNA strand (+ strand or − strand).

Typically, a reference sequence is referred to for a particular sequence. Alleles that differ from the reference are sometimes referred to as "variant" alleles. A variant sequence, as used herein, refers to a sequence that differs from the reference sequence but is otherwise substantially similar. Alleles at the polymorphic genetic markers described herein are variants. Additional variants can include changes that affect a polypeptide. Sequence differences, when compared to a reference nucleotide sequence, can include the insertion or deletion of a single nucleotide, or of more than one nucleotide, resulting in a frame shift; the change of at least one nucleotide, resulting in a change in the encoded amino acid; the change of at least one nucleotide, resulting in the generation of a premature stop codon; the deletion of several nucleotides, resulting in a deletion of one or more amino acids encoded by the nucleotides; the insertion of one or several nucleotides, such as by unequal recombination or gene conversion, resulting in an interruption of the coding sequence of a reading frame; duplication of all or a part of a sequence; transposition; or a rearrangement of a nucleotide sequence. Such sequence changes can alter the polypeptide encoded by the nucleic acid. For example, if the change in the nucleic acid sequence causes a frame shift, the frame shift can result in a change in the encoded amino acids, and/or can result in the generation of a premature stop codon, causing generation of a truncated polypeptide. Alternatively, a polymorphism associated with a disease or trait can be a synonymous change in one or more nucleotides (i.e., a change that does not result in a change in the amino acid sequence). Such a polymorphism can, for example, alter splice sites, affect the stability or transport of mRNA, or otherwise affect the transcription or translation of an encoded polypeptide. It can also alter DNA to increase the possibility that structural changes, such as amplifications or deletions, occur at the somatic level. The polypeptide encoded by the reference nucleotide sequence is the "reference" polypeptide with a particular reference amino acid sequence, and polypeptides encoded by variant alleles are referred to as "variant" polypeptides with variant amino acid sequences.

A haplotype refers to a segment of DNA that is characterized by a specific combination of alleles arranged along the segment. For diploid organisms such as humans, a haplotype comprises one member of the pair of alleles for each polymorphic marker or locus. In a certain embodiment, the haplotype can comprise two or more alleles, three or more alleles, four or more alleles, or five or more alleles, each allele corresponding to a specific polymorphic marker along the segment. Haplotypes can comprise a combination of various polymorphic markers, e.g., SNPs and microsatellites, having

particular alleles at the polymorphic sites. The haplotypes thus comprise a combination of alleles at various genetic markers.

Detecting specific polymorphic markers and/or haplotypes can be accomplished by methods known in the art for detecting sequences at polymorphic sites. For example, standard techniques for genotyping for the presence of SNPs and/or microsatellite markers can be used, such as fluorescence-based techniques (Chen, X. et al., *Genome Res.* 9(5): 492-98 (1999); Kutyavin et al., *Nucleic Acid Res.* 34:e128 (2006)), utilizing PCR, LCR, Nested PCR and other techniques for nucleic acid amplification. Specific methodologies available for SNP genotyping include, but are not limited to, TaqMan genotyping assays and SNPlex platforms (Applied Biosystems), mass spectrometry (e.g., MassARRAY system from Sequenom), minisequencing methods, real-time PCR, Bio-Plex system (BioRad), CEQ and SNPstream systems (Beckman), Molecular Inversion Probe array technology (e.g., Affymetrix GeneChip), and BeadArray Technologies (e.g., Illumina GoldenGate and Infinium assays). By these or other methods available to the person skilled in the art, one or more alleles at polymorphic markers, including microsatellites, SNPs or other types of polymorphic markers, can be identified.

In the present context, and individual who is at an increased susceptibility (i.e., increased risk) for a disease, is an individual in whom at least one specific allele at one or more polymorphic marker or haplotype conferring increased susceptibility (increased risk) for the disease is identified (i.e., at-risk marker alleles or haplotypes). The at-risk marker or haplotype is one that confers an increased risk (increased susceptibility) of the disease. In one embodiment, significance associated with a marker or haplotype is measured by a relative risk (RR). In another embodiment, significance associated with a marker or haplotye is measured by an odds ratio (OR). In a further embodiment, the significance is measured by a percentage. In one embodiment, a significant increased risk is measured as a risk (relative risk and/or odds ratio) of at least 1.2, including but not limited to: at least 1.2, at least 1.3, at least 1.4, at least 1.5, at least 1.6, at least 1.7, 1.8, at least 1.9, at least 2.0, at least 2.5, at least 3.0, at least 4.0, and at least 5.0. In a particular embodiment, a risk (relative risk and/or odds ratio) of at least 1.2 is significant. In another particular embodiment, a risk of at least 1.3 is significant. In yet another embodiment, a risk of at least 1.4 is significant. In a further embodiment, a relative risk of at least 1.5 is significant. In another further embodiment, a significant increase in risk is at least 1.7 is significant. However, other cutoffs are also contemplated, e.g., at least 1.15, 1.25, 1.35, and so on, and such cutoffs are also within scope of the present invention. In other embodiments, a significant increase in risk is at least about 20%, including but not limited to about 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 150%, 200%, 300%, and 500%. In one particular embodiment, a significant increase in risk is at least 20%. In other embodiments, a significant increase in risk is at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90% and at least 100%. Other cutoffs or ranges as deemed suitable by the person skilled in the art to characterize the invention are however also contemplated, and those are also within scope of the present invention. In certain embodiments, a significant increase in risk is characterized by a p-value, such as a p-value of less than 0.05, less than 0.01, less than 0.001, less than 0.0001, less than 0.00001, less than 0.000001, less than 0.0000001, less than 0.00000001, or less than 0.000000001.

An at-risk polymorphic marker or haplotype of the present invention is one where at least one allele of at least one marker or haplotype is more frequently present in an individual at risk for the disease or trait (affected), compared to the frequency of its presence in a comparison group (control), and wherein the presence of the marker or haplotype is indicative of susceptibility to the disease or trait. The control group may in one embodiment be a population sample, i.e. a random sample from the general population. In another embodiment, the control group is represented by a group of individuals who are disease-free. Such disease-free control may in one embodiment be characterized by the absence of one or more specific disease-associated symptoms. In another embodiment, the disease-free control group is characterized by the absence of one or more disease-specific risk factors. Such risk factors are in one embodiment at least one environmental risk factor. Representative environmental factors are natural products, minerals or other chemicals which are known to affect, or contemplated to affect, the risk of developing the specific disease or trait. Other environmental risk factors are risk factors related to lifestyle, including but not limited to food and drink habits, geographical location of main habitat, and occupational risk factors. In another embodiment, the risk factors are at least one genetic risk factor.

As an example of a simple test for correlation would be a Fisher-exact test on a two by two table. Given a cohort of chromosomes, the two by two table is constructed out of the number of chromosomes that include both of the markers or haplotypes, one of the markers or haplotypes but not the other and neither of the markers or haplotypes.

In other embodiments of the invention, an individual who is at a decreased susceptibility (i.e., at a decreased risk) for a disease or trait is an individual in whom at least one specific allele at one or more polymorphic marker or haplotype conferring decreased susceptibility for the disease or trait is identified. The marker alleles and/or haplotypes conferring decreased risk are also said to be protective. In one aspect, the protective marker or haplotype is one that confers a significant decreased risk (or susceptibility) of the disease or trait. In one embodiment, significant decreased risk is measured as a relative risk of less than 0.9, including but not limited to less than 0.9, less than 0.8, less than 0.7, less than 0.6, less than 0.5, less than 0.4, less than 0.3, less than 0.2 and less than 0.1. In one particular embodiment, significant decreased risk is less than 0.7. In another embodiment, significant decreased risk is less than 0.5. In yet another embodiment, significant decreased risk is less than 0.3. In another embodiment, the decrease in risk (or susceptibility) is at least 20%, including but not limited to at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% and at least 98%. In one particular embodiment, a significant decrease in risk is at least about 30%. In another embodiment, a significant decrease in risk is at least about 50%. In another embodiment, the decrease in risk is at least about 70%. Other cutoffs or ranges as deemed suitable by the person skilled in the art to characterize the invention are however also contemplated, and those are also within scope of the present invention.

The person skilled in the art will appreciate that for markers with two alleles present in the population being studied (such as SNPs), and wherein one allele is found in increased frequency in a group of individuals with a trait or disease in the population, compared with controls, the other allele of the marker will be found in decreased frequency in the group of individuals with the trait or disease, compared with controls. In such a case, one allele of the marker (the one found in

increased frequency in individuals with the trait or disease) will be the at-risk allele, while the other allele will be a protective allele.

A genetic variant associated with a disease or a trait can be used alone to predict the risk of the disease for a given genotype. For a biallelic marker, such as a SNP, there are 3 possible genotypes: homozygote for the at risk variant, heterozygote, and non carrier of the at risk variant. Risk associated with variants at multiple loci can be used to estimate overall risk. For multiple SNP variants, there are k possible genotypes $k=3^n\times2^p$; where n is the number autosomal loci and p the number of gonosomal (sex chromosomal) loci. Overall risk assessment calculations for a plurality of risk variants usually assume that the relative risks of different genetic variants multiply, i.e. the overall risk (e.g., RR or OR) associated with a particular genotype combination is the product of the risk values for the genotype at each locus. If the risk presented is the relative risk for a person, or a specific genotype for a person, compared to a reference population with matched gender and ethnicity, then the combined risk—is the product of the locus specific risk values—and which also corresponds to an overall risk estimate compared with the population. If the risk for a person is based on a comparison to non-carriers of the at risk allele, then the combined risk corresponds to an estimate that compares the person with a given combination of genotypes at all loci to a group of individuals who do not carry risk variants at any of those loci. The group of non-carriers of any at risk variant has the lowest estimated risk and has a combined risk, compared with itself (i.e., non-carriers) of 1.0, but has an overall risk, compare with the population, of less than 1.0. It should be noted that the group of non-carriers can potentially be very small, especially for large number of loci, and in that case, its relevance is correspondingly small.

The multiplicative model is a parsimonious model that usually fits the data of complex traits reasonably well. Deviations from multiplicity have been rarely described in the context of common variants for common diseases, and if reported are usually only suggestive since very large sample sizes are usually required to be able to demonstrate statistical interactions between loci.

By way of an example, let us consider variants in eight regions (loci) that have been described to associate with prostate cancer (Gudmundsson, J., et al., *Nat Genet* 39:631-7 (2007), Gudmundsson, J., et al., *Nat Genet* 39:977-83 (2007); Yeager, M., et al, *Nat Genet* 39:645-49 (2007), Amundadottir, L., et al., *Nat Genet* 38:652-8 (2006); Haiman, C. A., et al., *Nat Genet* 39:638-44 (2007)). Seven of these loci are on autosomes, and the remaining locus is on chromosome X. The total number of theoretical genotypic combinations is then $3^7\times2^1=4374$. Some of those genotypic classes are very rare, but are still possible, and should be considered for overall risk assessment. It is likely that the multiplicative model applied in the case of multiple genetic variant will also be valid in conjugation with non-genetic risk variants assuming that the genetic variant does not clearly correlate with the "environmental" factor. In other words, genetic and non-genetic at-risk variants can be assessed under the multiplicative model to estimate combined risk, assuming that the non-genetic and genetic risk factors do not interact.

Accordingly, in certain embodiments, therefore, the markers shown herein to be predictive of risk of prostate cancer in humans can be used in combination with any one, or a combination of, rs2710646 allele A, rs16901979 allele A, rs1447295 allele A, rs6983267 allele G, rs10896450 allele G, rs1859962 allele G, rs4430796 allele A and rs5945572 allele A. In a preferred embodiment, the at-risk markers for prostate cancer as described herein are assessed together with rs2710646 allele A, rs16901979 allele A, rs1447295 allele A, rs6983267 allele G, rs10896450 allele G, rs1859962 allele G, rs4430796 allele A and rs5945572 allele A to determine overall risk of prostate cancer in an individual.

The skilled person will realize that the markers presented herein may also be assessed in combination with any other genetic risk factors for prostate cancer and/or colorectal cancer, so as to determine overall risk of the cancer in an individual.

Linkage Disequilibrium

The natural phenomenon of recombination, which occurs on average once for each chromosomal pair during each meiotic event, represents one way in which nature provides variations in sequence (and biological function by consequence). It has been discovered that recombination does not occur randombly in the genome; rather, there are large variations in the frequency of recombination rates, resulting in small regions of high recombination frequency (also called recombination hotspots) and larger regions of low recombination frequency, which are commonly referred to as Linkage Disequilibrium (LD) blocks (Myers, S. et al., *Biochem Soc Trans* 34:526-530 (2006); Jeffreys, A. J., et al., *Nature Genet.* 29:217-222 (2001); May, C. A., et al., *Nature Genet* 31:272-275 (2002)).

Linkage Disequilibrium (LD) refers to a non-random assortment of two genetic elements. For example, if a particular genetic element (e.g., an allele of a polymorphic marker, or a haplotype) occurs in a population at a frequency of 0.50 (50%) and another element occurs at a frequency of 0.50 (50%), then the predicted occurrance of a person's having both elements is 0.25 (25%), assuming a random distribution of the elements. However, if it is discovered that the two elements occur together at a frequency higher than 0.25, then the elements are said to be in linkage disequilibrium, since they tend to be inherited together at a higher rate than what their independent frequencies of occurrence (e.g., allele or haplotype frequencies) would predict. Roughly speaking, LD is generally correlated with the frequency of recombination events between the two elements. Allele or haplotype frequencies can be determined in a population by genotyping individuals in a population and determining the frequency of the occurence of each allele or haplotype in the population. For populations of diploids, e.g., human populations, individuals will typically have two alleles for each genetic element (e.g., a marker, haplotype or gene).

Many different measures have been proposed for assessing the strength of linkage disequilibrium (LD; reviewed in Devlin, B. & Risch, N., *Genomics* 29:311-22 (1995))). Most capture the strength of association between pairs of biallelic sites. Two important pairwise measures of LD are r^2 (sometimes denoted Δ^2) and |D'| (Lewontin, R., *Genetics* 49:49-67 (1964); Hill, W. G. & Robertson, A. *Theor. Appl. Genet.* 22:226-231 (1968)). Both measures range from 0 (no disequilibrium) to 1 ('complete' disequilibrium), but their interpretation is slightly different. |D'| is defined in such a way that it is equal to 1 if just two or three of the possible haplotypes are present, and it is <1 if all four possible haplotypes are present. Therefore, a value of |D'| that is <1 indicates that historical recombination may have occurred between two sites (recurrent mutation can also cause |D'| to be <1, but for single nucleotide polymorphisms (SNPs) this is usually regarded as being less likely than recombination). The measure r^2 represents the statistical correlation between two sites, and takes the value of 1 if only two haplotypes are present.

The r^2 measure is arguably the most relevant measure for association mapping, because there is a simple inverse relationship between r^2 and the sample size required to detect association between susceptibility loci and SNPs. These mea-

sures are defined for pairs of sites, but for some applications a determination of how strong LD is across an entire region that contains many polymorphic sites might be desirable (e.g., testing whether the strength of LD differs significantly among loci or across populations, or whether there is more or less LD in a region than predicted under a particular model). Measuring LD across a region is not straightforward, but one approach is to use the measure r, which was developed in population genetics. Roughly speaking, r measures how much recombination would be required under a particular population model to generate the LD that is seen in the data. This type of method can potentially also provide a statistically rigorous approach to the problem of determining whether LD data provide evidence for the presence of recombination hotspots. For the methods described herein, a significant r^2 value can be at least 0.1 such as at least 0.1, 0.15, 0.2, 0.25, 0.3, 0.35, 0.4, 0.45, 0.5, 0.55, 0.6, 0.65, 0.7, 0.75, 0.8, 0.85, 0.9, 0.91, 0.92, 0.93, 0.94, 0.95, 0.96, 0.97, 0.98, 0.99 or 1.0. In one preferred embodiment, the significant r^2 value can be at least 0.2. Alternatively, linkage disequilibrium as described herein, refers to linkage disequilibrium characterized by values of |D'| of at least 0.2, such as 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.85, 0.9, 0.95, 0.96, 0.97, 0.98, 0.99. Thus, linkage disequilibrium represents a correlation between alleles of distinct markers. It is measured by correlation coefficient or |D'| (r^2 up to 1.0 and |D'| up to 1.0). In certain embodiments, linkage disequilibrium is defined in terms of values for both the r^2 and |D'| measures. In one such embodiment, a significant linkage disequilibrium is defined as $r^2>0.2$ and/or |D'|>0.8. In another embodiment, a significant linkage disequilibrium is defined as $r^2>0.2$ and/or |D'|>0.9. Other combinations and permutations of values of r^2 and |D'| for determining linkage disequilibrium are also possible, and within the scope of the invention. Linkage disequilibrium can be determined in a single human population, as defined herein, or it can be determined in a collection of samples comprising individuals from more than one human population. In one embodiment of the invention, LD is determined in a sample from one or more of the HapMap populations (caucasian, african, japanese, chinese), as defined (http://www.hapmap.org). In one such embodiment, LD is determined in the CEU population of the HapMap samples. In another embodiment, LD is determined in the YRI population. In yet another embodiment, LD is determined in samples from the Icelandic population.

If all polymorphisms in the genome were identical at the population level, then every single one of them would need to be investigated in association studies. However, due to linkage disequilibrium between polymorphisms, tightly linked polymorphisms are strongly correlated, which reduces the number of polymorphisms that need to be investigated in an association study to observe a significant association. Another consequence of LD is that many polymorphisms may give an association signal due to the fact that these polymorphisms are strongly correlated.

Genomic LD maps have been generated across the genome, and such LD maps have been proposed to serve as framework for mapping disease-genes (Risch, N. & Merkiangas, K, *Science* 273:1516-1517 (1996); Maniatis, N., et al., *Proc Natl Acad Sci USA* 99:2228-2233 (2002); Reich, D E et al, *Nature* 411:199-204 (2001)).

It is now established that many portions of the human genome can be broken into series of discrete haplotype blocks containing a few common haplotypes; for these blocks, linkage disequilibrium data provides little evidence indicating recombination (see, e.g., Wall., J. D. and Pritchard, J. K., *Nature Reviews Genetics* 4:587-597 (2003); Daly, M. et al., *Nature Genet.* 29:229-232 (2001); Gabriel, S. B. et al., *Science* 296:2225-2229 (2002); Patil, N. et al., *Science* 294:1719-1723 (2001); Dawson, E. et al., *Nature* 418:544-548 (2002); Phillips, M. S. et al., *Nature Genet.* 33:382-387 (2003)).

There are two main methods for defining these haplotype blocks: blocks can be defined as regions of DNA that have limited haplotype diversity (see, e.g., Daly, M. et al., *Nature Genet.* 29:229-232 (2001); Patil, N. et al., *Science* 294:1719-1723 (2001); Dawson, E. et al., *Nature* 418:544-548 (2002); Zhang, K. et al., *Proc. Natl. Acad. Sci. USA* 99:7335-7339 (2002)), or as regions between transition zones having extensive historical recombination, identified using linkage disequilibrium (see, e.g., Gabriel, S. B. et al., *Science* 296:2225-2229 (2002); Phillips, M. S. et al., *Nature Genet.* 33:382-387 (2003); Wang, N. et al., *Am. J. Hum. Genet.* 71:1227-1234 (2002); Stumpf, M. P., and Goldstein, D. B., *Curr. Biol.* 13:1-8 (2003)). More recently, a fine-scale map of recombination rates and corresponding hotspots across the human genome has been generated (Myers, S., et al., *Science* 310:321-32324 (2005); Myers, S. et al., *Biochem Soc Trans* 34:526530 (2006)). The map reveals the enormous variation in recombination across the genome, with recombination rates as high as 10-60 cM/Mb in hotspots, while closer to 0 in intervening regions, which thus represent regions of limited haplotype diversity and high LD. The map can therefore be used to define haplotype blocks/LD blocks as regions flanked by recombination hotspots. As used herein, the terms "haplotype block" or "LD block" includes blocks defined by any of the above described characteristics, or other alternative methods used by the person skilled in the art to define such regions.

Haplotype blocks can be used to map associations between phenotype and haplotype status, using single markers or haplotypes comprising a plurality of markers. The main haplotypes can be identified in each haplotype block, and then a set of "tagging" SNPs or markers (the smallest set of SNPs or markers needed to distinguish among the haplotypes) can then be identified. These tagging SNPs or markers can then be used in assessment of samples from groups of individuals, in order to identify association between phenotype and haplotype. If desired, neighboring haplotype blocks can be assessed concurrently, as there may also exist linkage disequilibrium among the haplotype blocks.

It has thus become apparent that for any given observed association to a polymorphic marker in the genome, it is likely that additional markers in the genome also show association. This is a natural consequence of the uneven distribution of LD across the genome, as observed by the large variation in recombination rates. The markers used to detect association thus in a sense represent "tags" for a genomic region (i.e., a haplotype block or LD block) that is associating with a given disease or trait, and as such are useful for use in the methods and kits of the present invention. One or more causative (functional) variants or mutations may reside within the region found to be associating to the disease or trait. The functional variant may be another SNP, a tandem repeat polymorphism (such as a minisatellite or a microsatellite), a transposable element, or a copy number variation, such as an inversion, deletion or insertion. Such variants in LD with the variants described herein may confer a higher relative risk (RR) or odds ratio (OR) than observed for the tagging markers used to detect the association. The present invention thus refers to the markers used for detecting association to the disease, as described herein, as well as markers in linkage disequilibrium with the markers. Thus, in certain embodiments of the invention, markers that are in LD with the markers and/or haplotypes of the invention, as described herein,

may be used as surrogate markers. The surrogate markers have in one embodiment relative risk (RR) and/or odds ratio (OR) values smaller than for the markers or haplotypes initially found to be associating with the disease, as described herein. In other embodiments, the surrogate markers have RR or OR values greater than those initially determined for the markers initially found to be associating with the disease, as described herein. An example of such an embodiment would be a rare, or relatively rare (such as <10% allelic population frequency) variant in LD with a more common variant (>10% population frequency) initially found to be associating with the disease, such as the variants described herein. Identifying and using such markers for detecting the association discovered by the inventors as described herein can be performed by routine methods well known to the person skilled in the art, and are therefore within the scope of the present invention.

Determination of Haplotype Frequency

The frequencies of haplotypes in patient and control groups can be estimated using an expectation-maximization algorithm (Dempster A. et al., *J. R. Stat. Soc. B,* 39:1-38 (1977)). An implementation of this algorithm that can handle missing genotypes and uncertainty with the phase can be used. Under the null hypothesis, the patients and the controls are assumed to have identical frequencies. Using a likelihood approach, an alternative hypothesis is tested, where a candidate at-risk-haplotype, which can include the markers described herein, is allowed to have a higher frequency in patients than controls, while the ratios of the frequencies of other haplotypes are assumed to be the same in both groups. Likelihoods are maximized separately under both hypotheses and a corresponding 1-df likelihood ratio statistic is used to evaluate the statistical significance.

To look for at-risk and protective markers and haplotypes within a linkage region, for example, association of all possible combinations of genotyped markers is studied, provided those markers span a practical region. The combined patient and control groups can be randomly divided into two sets, equal in size to the original group of patients and controls. The marker and haplotype analysis is then repeated and the most significant p-value registered is determined. This randomization scheme can be repeated, for example, over 100 times to construct an empirical distribution of p-values. In a preferred embodiment, a p-value of <0.05 is indicative of a significant marker and/or haplotype association.

Haplotype Analysis

One general approach to haplotype analysis involves using likelihood-based inference applied to NEsted MOdels (Gretarsdottir S., et al., *Nat. Genet.* 35:131-38 (2003)). The method is implemented in the program NEMO, which allows for many polymorphic markers, SNPs and microsatellites. The method and software are specifically designed for case-control studies where the purpose is to identify haplotype groups that confer different risks. It is also a tool for studying LD structures. In NEMO, maximum likelihood estimates, likelihood ratios and p-values are calculated directly, with the aid of the EM algorithm, for the observed data treating it as a missing-data problem.

Even though likelihood ratio tests based on likelihoods computed directly for the observed data, which have captured the information loss due to uncertainty in phase and missing genotypes, can be relied on to give valid p-values, it would still be of interest to know how much information had been lost due to the information being incomplete. The information measure for haplotype analysis is described in Nicolae and Kong (Technical Report 537, Department of Statistics, University of Statistics, University of Chicago; *Biometrics,* 60(2):368-75 (2004)) as a natural extension of information measures defined for linkage analysis, and is implemented in NEMO.

For single marker association to a disease, the Fisher exact test can be used to calculate two-sided p-values for each individual allele. Usually, all p-values are presented unadjusted for multiple comparisons unless specifically indicated. The presented frequencies (for microsatellites, SNPs and haplotypes) are allelic frequencies as opposed to carrier frequencies. To minimize any bias due to the relatedness of patients who were recruited as families, first and second-degree relatives can be eliminated from the patient list. Furthermore, the test can be repeated for association correcting for any remaining relatedness among the patients, by extending a variance adjustment procedure described in Risch, N. & Teng, J. (*Genome Res.,* 8:1273-1288 (1998)), DNA pooling (ibid) for sibships so that it can be applied to general familial relationships, and present both adjusted and unadjusted p-values for comparison. The differences are in general very small as expected. To assess the significance of single-marker association corrected for multiple testing we can carry out a randomization test using the same genotype data. Cohorts of patients and controls can be randomized and the association analysis redone multiple times (e.g., up to 500,000 times) and the p-value is the fraction of replications that produced a p-value for some marker allele that is lower than or equal to the p-value we observed using the original patient and control cohorts.

For both single-marker and haplotype analyses, relative risk (RR) and the population attributable risk (PAR) can be calculated assuming a multiplicative model (haplotype relative risk model) (Terwilliger, J. D. & Ott, J., *Hum. Hered.* 42:337-46 (1992) and Falk, C. T. & Rubinstein, P, *Ann. Hum. Genet.* 51 (Pt 3):227-33 (1987)), i.e., that the risks of the two alleles/haplotypes a person carries multiply. For example, if RR is the risk of A relative to a, then the risk of a person homozygote AA will be RR times that of a heterozygote Aa and RR^2 times that of a homozygote aa. The multiplicative model has a nice property that simplifies analysis and computations—haplotypes are independent, i.e., in Hardy-Weinberg equilibrium, within the affected population as well as within the control population. As a consequence, haplotype counts of the affecteds and controls each have multinomial distributions, but with different haplotype frequencies under the alternative hypothesis. Specifically, for two haplotypes, h_i and h_j, $\text{risk}(h_i)/\text{risk}(h_j)=(f_i/p_i)/(f_j/p_j)$, where f and p denote, respectively, frequencies in the affected population and in the control population. While there is some power loss if the true model is not multiplicative, the loss tends to be mild except for extreme cases. Most importantly, p-values are always valid since they are computed with respect to null hypothesis.

An association signal detected in one association study may be replicated in a second cohort, ideally from a different population (e.g., different region of same country, or a different country) of the same or different ethnicity. The advantage of replication studies is that the number of tests performed in the replication study is usually quite small, and hence the less stringent the statistical measure that needs to be applied. For example, for a genome-wide search for susceptibility variants for a particular disease or trait using 300,000 SNPs, a correction for the 300,000 tests performed (one for each SNP) can be performed. Since many SNPs on the arrays typically used are correlated (i.e., in LD), they are not independent. Thus, the correction is conservative. Nevertheless, applying this correction factor requires an observed P-value of less than $0.05/300{,}000=1.7\times10^{-7}$ for the signal to be considered significant applying this conservative test on results from a

single study cohort. Obviously, signals found in a genome-wide association study with P-values less than this conservative threshold are a measure of a true genetic effect, and replication in additional cohorts is not necessarily from a statistical point of view. Importantly, however, signals with P-values that are greater than this threshold may also be due to a true genetic effect. Thus, since the correction factor depends on the number of statistical tests performed, if one signal (one SNP) from an initial study is replicated in a second case-control cohort, the appropriate statistical test for significance is that for a single statistical test, i.e., P-value less than 0.05. Replication studies in one or even several additional case-control cohorts have the added advantage of providing assessment of the association signal in additional populations, thus simultaneously confirming the initial finding and providing an assessment of the overall significance of the genetic variant(s) being tested in human populations in general.

The results from several case-control cohorts can also be combined to provide an overall assessment of the underlying effect. The methodology commonly used to combine results from multiple genetic association studies is the Mantel-Haenszel model (Mantel and Haenszel, *J Natl Cancer Inst* 22:719-48 (1959)). The model is designed to deal with the situation where association results from different populations, with each possibly having a different population frequency of the genetic variant, are combined. The model combines the results assuming that the effect of the variant on the risk of the disease, a measured by the OR or RR, is the same in all populations, while the frequency of the variant may differ between the populations. Combining the results from several populations has the added advantage that the overall power to detect a real underlying association signal is increased, due to the increased statistical power provided by the combined cohorts. Furthermore, any deficiencies in individual studies, for example due to unequal matching of cases and controls or population stratification will tend to balance out when results from multiple cohorts are combined, again providing a better estimate of the true underlying genetic effect.

Risk Assessment and Diagnostics

Within any given population, there is an absolute risk of developing a disease or trait, defined as the chance of a person developing the specific disease or trait over a specified time-period. For example, a woman's lifetime absolute risk of breast cancer is one in nine. That is to say, one woman in every nine will develop breast cancer at some point in their lives. Risk is typically measured by looking at very large numbers of people, rather than at a particular individual. Risk is often presented in terms of Absolute Risk (AR) and Relative Risk (RR). Relative Risk is used to compare risks associating with two variants or the risks of two different groups of people. For example, it can be used to compare a group of people with a certain genotype with another group having a different genotype. For a disease, a relative risk of 2 means that one group has twice the chance of developing a disease as the other group. The risk presented is usually the relative risk for a person, or a specific genotype of a person, compared to the population with matched gender and ethnicity. Risks of two individuals of the same gender and ethnicity could be compared in a simple manner. For example, if, compared to the population, the first individual has relative risk 1.5 and the second has relative risk 0.5, then the risk of the first individual compared to the second individual is 1.5/0.5=3.

As described herein, certain polymorphic markers and haplotypes comprising such markers are found to be useful for risk assessment of prostate cancer and colorectal cancer. Risk assessment can involve the use of the markers for diagnosing a susceptibility to prostate cancer and/or colorectal cancer. Particular alleles of polymorphic markers are found more frequently in individuals with prostate cancer and/or colorectal cancer, than in individuals without diagnosis of prostate cancer and/or colorectal cancer. Therefore, these marker alleles have predictive value for detecting prostate cancer and/or colorectal cancer, or a susceptibility to prostate cancer and/or colorectal cancer, in an individual. Tagging markers in linkage disequilibrium with the at-risk variants (or protective variants) described herein can be used as surrogates for these markers (and/or haplotypes). Such surrogate markers can be located within a particular haplotype block or LD block, e.g. LD Block C11 or LD Block C06. Such surrogate markers can also sometimes be located outside the physical boundaries of such a haplotype block or LD block, either in close vicinity of the LD block/haplotype block, but possibly also located in a more distant genomic location.

Long-distance LD can for example arise if particular genomic regions (e.g., genes) are in a functional relationship. For example, if two genes encode proteins that play a role in a shared metabolic pathway, then particular variants in one gene may have a direct impact on observed variants for the other gene. Let us consider the case where a variant in one gene leads to increased expression of the gene product. To counteract this effect and preserve overall flux of the particular pathway, this variant may have led to selection of one (or more) variants at a second gene that confers decreased expression levels of that gene. These two genes may be located in different genomic locations, possibly on different chromosomes, but variants within the genes are in apparent LD, not because of their shared physical location within a region of high LD, but rather due to evolutionary forces. Such LD is also contemplated and within scope of the present invention. The skilled person will appreciate that many other scenarios of functional gene-gene interaction are possible, and the particular example discussed here represents only one such possible scenario.

Markers with values of r^2 equal to 1 are perfect surrogates for the at-risk variants, i.e. genotypes for one marker perfectly predicts genotypes for the other. Markers with smaller values of r^2 than 1 can also be surrogates for the at-risk variant, or alternatively represent variants with relative risk values as high as or possibly even higher than the at-risk variant. The at-risk variant identified may not be the functional variant itself, but is in this instance in linkage disequilibrium with the true functional variant. The functional variant may for example be a tandem repeat, such as a minisatellite or a microsatellite, a transposable element (e.g., an Alu element), or a structural alteration, such as a deletion, insertion or inversion (sometimes also called copy number variations, or CNVs). The present invention encompasses the assessment of such surrogate markers for the markers as disclosed herein. Such markers are annotated, mapped and listed in public databases, as well known to the skilled person, or can alternatively be readily identified by sequencing the region or a part of the region identified by the markers of the present invention in a group of individuals, and identify polymorphisms in the resulting group of sequences. As a consequence, the person skilled in the art can readily and without undue experimentation genotype surrogate markers in linkage disequilibrium with the markers and/or haplotypes as described herein. The tagging or surrogate markers in LD with the at-risk variants detected, also have predictive value for detecting association to prostate cancer and/or colorectal cancer, or a susceptibility to prostate cancer and/or colorectal cancer, in an individual. These tagging or surrogate markers that are in LD with the markers of the present invention can

also include other markers that distinguish among haplotypes, as these similarly have predictive value for detecting susceptibility to prostate cancer and/or colorectal cancer.

The present invention can in certain embodiments be practiced by assessing a sample comprising genomic DNA from an individual for the presence of variants described herein to be associated with cancer. Such assessment typically steps that detect the presence or absence of at least one allele of at least one polymorphic marker, using methods well known to the skilled person and further described herein, and based on the outcome of such assessment, determine whether the individual from whom the sample is derived is at increased or decreased risk (increased or decreased susceptibility) of cancer. Detecting particular alleles of polymorphic markers can in certain embodiments be done by obtaining nucleic acid sequence data for a particular human individual, that identifies at least one allele of at least one polymorphic marker. Different alleles of the at least one marker are associated with different susceptibility to the disease in humans. Obtaining nucleic acid sequence data can comprise nucleic acid sequence at a single nucleotide position, which is sufficient to identify alleles at polymorphic markers, such as SNPs and microsatellites. The nucleic acid sequence data can also comprise sequence at any other number of nucleotide positions, in particular for genetic markers that comprise multiple nucleotide positions, and can be anywhere from two to hundreds of thousands, possibly even millions, of nucleotides (in particular, in the case of copy number variations (CNVs)).

In certain embodiments, the invention can be practiced utilizing a dataset comprising information about the genotype status of at least one polymorphic marker associated with prostate and/or colorectal cancer (or markers in linkage disequilibrium with at least one marker associated with these diseases). In other words, a dataset containing information about such genetic status, for example in the form of genotype counts at a certain polymorphic marker, or a plurality of markers (e.g., an indication of the presence or absence of certain at-risk alleles), or actual genotypes for one or more markers, can be queried for the presence or absence of certain at-risk alleles at certain polymorphic markers shown by the present inventors to be associated with risk of prostate cancer and colorectal cancer. A positive result for a variant (e.g., marker allele) associated with the cancer is indicative of the individual from which the dataset is derived is at increased susceptibility (increased risk) of the cancer.

In certain embodiments of the invention, a polymorphic marker is correlated to the cancer by referencing genotype data for the polymorphic marker to a look-up table that comprises correlations between at least one allele of the polymorphism and the cancer. In some embodiments, the table comprises a correlation for one polymorphism. In other embodiments, the table comprises a correlation for a plurality of polymorphisms. In both scenarios, by referencing to a look-up table that gives an indication of a correlation between a marker and the cancer, a risk for the cancer, or a susceptibility to the cancer, can be identified in the individual from whom the sample is derived. In some embodiments, the correlation is reported as a statistical measure. The statistical measure may be reported as a risk measure, such as a relative risk (RR), an absolute risk (AR) or an odds ratio (OR).

The markers of the invention, e.g., the markers presented in Tables 1-6, may be useful for risk assessment and diagnostic purposes for prostate cancer and/or colorectal cancer, either alone or in combination. Thus, even in cases where the increase in risk by individual markers is relatively modest, i.e. on the order of 10-30%, the association may have significant implications. Thus, relatively common variants may have significant contribution to the overall risk (Population Attributable Risk is high), or combination of markers can be used to define groups of individual who, based on the combined risk of the markers, is at significant combined risk of developing the disease.

Thus, in one embodiment of the invention, a plurality of variants (genetic markers, biomarkers and/or haplotypes) is used for overall risk assessment. These variants are in one embodiment selected from the variants as disclosed herein. Other embodiments include the use of the variants of the present invention in combination with other variants known to be useful for diagnosing a susceptibility to prostate cancer and/or colorectal cancer. In such embodiments, the genotype status of a plurality of markers and/or haplotypes is determined in an individual, and the status of the individual compared with the population frequency of the associated variants, or the frequency of the variants in clinically healthy subjects, such as age-matched and sex-matched subjects. Methods known in the art, such as multivariate analyses or joint risk analyses, may subsequently be used to determine the overall risk conferred based on the genotype status at the multiple loci. Assessment of risk based on such analysis may subsequently be used in the methods and kits of the invention, as described herein.

In certain embodiments of risk assessment of prostate cancer, the variants described herein to be associated with prostate cancer risk are assessed in combination with at least one marker selected from the group consisting of rs2710646, rs16901979, rs1447295, rs6983267, rs10896450, rs1859962, rs4430796 and rs5945572. Any combination of these markers, or surrogate markers in linkage disequilibrium therewith, with any of the variants described herein for risk assessment of prostate cancer is contemplated.

As described in the above, the haplotype block structure of the human genome has the effect that a large number of variants (markers and/or haplotypes) in linkage disequilibrium with the variant originally associated with a disease or trait may be used as surrogate markers for assessing association to the disease or trait. The number of such surrogate markers will depend on factors such as the historical recombination rate in the region, the mutational frequency in the region (i.e., the number of polymorphic sites or markers in the region), and the extent of LD (size of the LD block) in the region. These markers are usually located within the physical boundaries of the LD block or haplotype block in question as defined using the methods described herein (e.g., LD block C11 and/or LD block C06), or by other methods known to the person skilled in the art. However, sometimes marker and haplotype association is found to extend beyond the physical boundaries of the haplotype block as defined. Such markers and/or haplotypes may in those cases be also used as surrogate markers and/or haplotypes for the markers and/or haplotypes physically residing within the haplotype block as defined. As a consequence, markers and haplotypes in LD (typically characterized by r^2 greater than 0.1, such as r^2 greater than 0.2, including r^2 greater than 0.3, also including r^2 greater than 0.4) with the markers and haplotypes of the present invention are also within the scope of the invention, even if they are physically located beyond the boundaries of the haplotype block as defined. This includes markers that are described herein (e.g., Tables 1-6, e.g. Tables 3-4), but may also include other markers that are in strong LD (e.g., characterized by r^2 greater than 0.1 or 0.2 and/or $|D'|>0.8$) with one or more of the markers listed in Tables 1-6.

For the SNP markers described herein, the opposite allele to the allele found to be in excess in patients (at-risk allele) is found in decreased frequency in prostate cancer and/or col-

orectal cancer. These markers and haplotypes in LD and/or comprising such markers, are thus protective for prostate cancer and/or colorectal cancer, i.e. they confer a decreased risk or susceptibility of individuals carrying these markers and/or haplotypes developing prostate cancer and/or colorectal cancer.

Certain variants of the present invention, including certain haplotypes comprise, in some cases, a combination of various genetic markers, e.g., SNPs and microsatellites. Detecting haplotypes can be accomplished by methods known in the art and/or described herein for detecting sequences at polymorphic sites. Furthermore, correlation between certain haplotypes or sets of markers and disease phenotype can be verified using standard techniques. A representative example of a simple test for correlation would be a Fisher-exact test on a two by two table.

In specific embodiments, a marker allele or haplotype found to be associated with prostate cancer and/or colorectal cancer, (e.g., marker alleles as listed in Tables 1-6) is one in which the marker allele or haplotype is more frequently present in an individual at risk for prostate cancer and/or colorectal cancer (affected), compared to the frequency of its presence in a healthy individual (control), wherein the presence of the marker allele or haplotype is indicative of prostate cancer and/or colorectal cancer or a susceptibility to prostate cancer and/or colorectal cancer. In other embodiments, at-risk markers in linkage disequilibrium with one or more markers found to be associated with prostate cancer and/or colorectal cancer (e.g., marker alleles as listed in Tables 1-6) are tagging markers that are more frequently present in an individual at risk for prostate cancer and/or colorectal cancer (affected), compared to the frequency of their presence in a healthy individual (control), wherein the presence of the tagging markers is indicative of increased susceptibility to prostate cancer and/or colorectal cancer. In a further embodiment, at-risk markers alleles (i.e. conferring increased susceptibility) in linkage disequilibrium with one or more markers found to be associated with prostate cancer and/or colorectal cancer (e.g., marker alleles as listed in Table 1-6), are markers comprising one or more allele that is more frequently present in an individual at risk for prostate cancer and/or colorectal cancer, compared to the frequency of their presence in a healthy individual (control), wherein the presence of the markers is indicative of increased susceptibility to.

Study Population

In a general sense, the methods and kits of the invention can be utilized from samples containing genomic DNA from any source, i.e. any individual. In preferred embodiments, the individual is a human individual. The individual can be an adult, child, or fetus. The present invention also provides for assessing markers and/or haplotypes in individuals who are members of a target population. Such a target population is in one embodiment a population or group of individuals at risk of developing the disease, based on other genetic factors, biomarkers, biophysical parameters (e.g., weight, BMD, blood pressure), or general health and/or lifestyle parameters (e.g., history of prostate and/or colorectal cancer or other cancers, previous diagnosis of prostate and/or colorectal cancer, family history of prostate cancer and/or colorectal cancer).

The invention provides for embodiments that include individuals from specific age subgroups, such as those over the age of 40, over age of 45, or over age of 50, 55, 60, 65, 70, 75, 80, or 85. Other embodiments of the invention pertain to other age groups, such as individuals aged less than 85, such as less than age 80, less than age 75, or less than age 70, 65, 60, 55, 50, 45, 40, 35, or age 30. Other embodiments relate to individuals with age at onset of the disease in any of the age ranges described in the above. It is also contemplated that a range of ages may be relevant in certain embodiments, such as age at onset at more than age 45 but less than age 60. Other age ranges are however also contemplated, including all age ranges bracketed by the age values listed in the above. The invention furthermore relates to individuals of either gender, males or females.

The Icelandic population is a Caucasian population of Northern European ancestry. A large number of studies reporting results of genetic linkage and association in the Icelandic population have been published in the last few years. Many of those studies show replication of variants, originally identified in the Icelandic population as being associating with a particular disease, in other populations (Styrkarsdottir, U., et al. *N Engl J Med Apr.* 29, 2008 (Epub ahead of print); Thorgeirsson, T., et al. *Nature* 452:638-42 (2008); Gudmundsson, J., et al. *Nat Genet.* 40:281-3 (2008); Stacey, S, N., et al., *Nat Genet.* 39:865-69 (2007); Helgadottir, A., et al., *Science* 316:1491-93 (2007); Steinthorsdottir, V., et al., *Nat Genet.* 39:770-75 (2007); Gudmundsson, J., et al., *Nat Genet.* 39:631-37 (2007); Frayling, T M, *Nature Reviews Genet* 8:657-662 (2007); Amundadottir, L. T., et al., *Nat Genet.* 38:652-58 (2006); Grant, S. F., et al., *Nat Genet.* 38:320-23 (2006)). Thus, genetic findings in the Icelandic population have in general been replicated in other populations, including populations from Africa and Asia.

It is thus believed that the markers of the present invention found to be associated with risk of prostate cancer and colorectal cancer to show similar association in other human populations. Particular embodiments comprising individual human populations are thus also contemplated and within the scope of the invention. Such embodiments relate to human subjects that are from one or more human population including, but not limited to, Caucasian populations, European populations, American populations, Eurasian populations, Asian populations, Central/South Asian populations, East Asian populations, Middle Eastern populations, African populations, Hispanic populations, and Oceanian populations. European populations include, but are not limited to, Swedish, Norwegian, Finnish, Russian, Danish, Icelandic, Irish, Kelt, English, Scottish, Dutch, Belgian, French, German, Spanish, Portugues, Italian, Polish, Bulgarian, Slavic, Serbian, Bosnian, Chech, Greek and Turkish populations. The invention furthermore in other embodiments can be practiced in specific human populations that include Bantu, Mandenk, Yoruba, San, Mbuti Pygmy, Orcadian, Adygel, Russian, Sardinian, Tuscan, Mozabite, Bedouin, Druze, Palestinian, Balochi, Brahui, Makrani, Sindhi, Pathan, Burusho, Hazara, Uygur, Kalash, Han, Dai, Daur, Hezhen, Lahu, Miao, Orogen, She, Tujia, Tu, Xibo, Yi, Mongolan, Naxi, Cambodian, Japanese, Yakut, Melanesian, Papuan, Karitianan, Surui, Colmbian, Maya and Pima.

In one preferred embodiment, the invention relates to populations that include black African ancestry such as populations comprising persons of African descent or lineage. Black African ancestry may be determined by self reporting as African-Americans, Afro-Americans, Black Americans, being a member of the black race or being a member of the negro race. For example, African Americans or Black Americans are those persons living in North America and having origins in any of the black racial groups of Africa. In another example, self-reported persons of black African ancestry may have at least one parent of black African ancestry or at least one grandparent of black African ancestry.

The racial contribution in individual subjects may also be determined by genetic analysis. Genetic analysis of ancestry

may be carried out using unlinked microsatellite markers such as those set out in Smith et al. (*Am J Hum Genet* 74, 1001-13 (2004)).

In certain embodiments, the invention relates to markers and/or haplotypes identified in specific populations, as described in the above. The person skilled in the art will appreciate that measures of linkage disequilibrium (LD) may give different results when applied to different populations. This is due to different population history of different human populations as well as differential selective pressures that may have led to differences in LD in specific genomic regions. It is also well known to the person skilled in the art that certain markers, e.g. SNP markers, have different population frequency in different populations, or are polymorphic in one population but not in another. The person skilled in the art will however apply the methods available and as thought herein to practice the present invention in any given human population. This may include assessment of polymorphic markers in the LD region of the present invention, so as to identify those markers that give strongest association within the specific population. Thus, the at-risk variants of the present invention may reside on different haplotype background and in different frequencies in various human populations. However, utilizing methods known in the art and the markers of the present invention, the invention can be practiced in any given human population.

Utility of Genetic Testing

The person skilled in the art will appreciate and understand that the variants described herein in general do not, by themselves, provide an absolute identification of individuals who will develop a particular disease. The variants described herein do however indicate increased and/or decreased likelihood that individuals carrying the at-risk or protective variants of the invention will develop symptoms associated with prostate cancer and/or colorectal cancer. This information is however extremely valuable in itself, as outlined in more detail in the below, as it can be used to, for example, initiate preventive measures at an early stage, perform regular physical and/or mental exams to monitor the progress and/or appearance of symptoms, or to schedule exams at a regular interval to identify the condition in question, so as to be able to apply treatment at an early stage.

The knowledge of a genetic variant that confers a risk of developing cancer offers the opportunity to apply a genetic-test to distinguish between individuals with increased risk of developing the cancer (i.e. carriers of the at-risk variant) and those with decreased risk of developing the cancer (i.e. carriers of the protective variant, or non-carriers of the at-risk variant). The core values of genetic testing, for individuals belonging to both of the above mentioned groups, are the possibilities of being able to diagnose the cancer at an early stage and provide information to the clinician about prognosis/aggressiveness of the disease in order to be able to apply the most appropriate treatment. For example, the application of a genetic test for cancer (e.g., colorectal cancer or prostate cancer (including aggressive or high Gleason grade prostate cancer, less aggressive or low Gleason grade prostate cancer)) can provide an opportunity for the detection of the cancer at an earlier stage which may lead to the application of therapeutic measures at an earlier stage, and thus can minimize the deleterious effects of the symptoms and serious health consequences conferred by cancer. Some advantages of genetic tests for prostate cancer include:

1. To Aid Early Detection

The application of a genetic test for prostate cancer can provide an opportunity for the detection of the disease at an earlier stage which leads to higher cure rates, if found locally, and increases survival rates by minimizing regional and distant spread of the tumor. For prostate cancer, a genetic test will most likely increase the sensitivity and specificity of the already generally applied Prostate Specific Antigen (PSA) test and Digital Rectal Examination (DRE). This can lead to lower rates of false positives (thus minimize unnecessary procedures such as needle biopsies) and false negatives (thus increasing detection of occult disease and minimizing morbidity and mortality due to PCA).

2. To Determine Aggressiveness

Genetic testing can provide information about pre-diagnostic prognostic indicators and enable the identification of individuals at high or low risk for aggressive tumor types that can lead to modification in screening strategies. For example, an individual determined to be a carrier of a high risk allele for the development of aggressive prostate cancer will likely undergo more frequent PSA testing, examination and have a lower threshold for needle biopsy in the presence of an abnormal PSA value.

Furthermore, identifying individuals that are carriers of high or low risk alleles for aggressive tumor types will lead to modification in treatment strategies. For example, if prostate cancer is diagnosed in an individual that is a carrier of an allele that confers increased risk of developing an aggressive form of prostate cancer, then the clinician would likely advise a more aggressive treatment strategy such as a prostatectomy instead of a less aggressive treatment strategy.

As is known in the art, Prostate Specific Antigen (PSA) is a protein that is secreted by the epithelial cells of the prostate gland, including cancer cells. An elevated level in the blood indicates an abnormal condition of the prostate, either benign or malignant. PSA is used to detect potential problems in the prostate gland and to follow the progress of prostate cancer therapy. PSA levels above 4 ng/ml are indicative of the presence of prostate cancer (although as known in the art and described herein, the test is neither very specific nor sensitive).

In one embodiment, the method of the invention is performed in combination with (either prior to, concurrently or after) a PSA assay. In a particular embodiment, the presence of an at-risk marker or haplotype, in conjunction with the subject having a PSA level greater than 4 ng/ml, is indicative of a more aggressive prostate cancer and/or a worse prognosis. As described herein, particular markers and haplotypes are associated with high Gleason (i.e., more aggressive) prostate cancer. In another embodiment, the presence of a marker or haplotype, in a patient who has a normal PSA level (e.g., less than 4 ng/ml), is indicative of a high Gleason (i.e., more aggressive) prostate cancer and/or a worse prognosis. A "worse prognosis" or "bad prognosis" occurs when it is more likely that the cancer will grow beyond the boundaries of the prostate gland, metastasize, escape therapy and/or kill the host.

In one embodiment, the presence of a marker or haplotype is indicative of a predisposition to a somatic rearrangement (e.g., one or more of an amplification, a translocation, an insertion and/or deletion) in a tumor or its precursor. The somatic rearrangement itself may subsequently lead to a more aggressive form of prostate cancer (e.g., a higher histologic grade, as reflected by a higher Gleason score or higher stage at diagnosis, an increased progression of prostate cancer (e.g., to a higher stage), a worse outcome (e.g., in terms of morbidity, complications or death)). As is known in the art, the Gleason grade is a widely used method for classifying prostate cancer tissue for the degree of loss of the normal glandular architecture (size, shape and differentiation of glands). A grade from 1-5 is assigned successively to each of the two

most predominant tissue patterns present in the examined tissue sample and are added together to produce the total or combined Gleason grade (scale of 2-10). High numbers indicate poor differentiation and therefore more aggressive cancer.

Aggressive prostate cancer is cancer that grows beyond the prostate, metastasizes and eventually kills the patient. As described herein, one surrogate measure of aggressiveness is a high combined Gleason grade. The higher the grade on a scale of 2-10 the more likely it is that a patient has aggressive disease.

The present invention furthermore relates to risk assessment for prostate cancer and colorectal cancer, including diagnosing whether an individual is at risk for developing prostate cancer and/or colorectal cancer. The polymorphic markers of the present invention can be used alone or in combination, as well as in combination with other factors, including other genetic risk factors or biomarkers, for risk assessment of an individual for prostate cancer and/or colorectal cancer. Certain factors known to affect the predisposition of an individual towards developing risk of developing common disease, including prostate cancer and/or colorectal cancer are known to the person skilled in the art and can be utilized in such assessment. These include, but are not limited to, age, gender, smoking status, family history of cancer, previously diagnosed cancer, colonic adenomas, chronic inflammatory bowel disease and diet. Methods known in the art can be used for such assessment, including multivariate analyses or logistic regression.

Methods

Methods for risk assessment of and risk management of prostate cancer and/or colorectal cancer are described herein and are encompassed by the invention. The invention also encompasses methods of assessing an individual for probability of response to a therapeutic agent for prostate cancer and/or colorectal cancer, as well as methods for predicting the effectiveness of a therapeutic agent for prostate cancer and/or colorectal cancer. Kits for assaying a sample from a subject to detect susceptibility to prostate cancer and/or colorectal cancer are also encompassed by the invention.

Diagnostic and Screening Methods

In certain embodiments, the present invention pertains to methods of diagnosing, or aiding in the diagnosis of, prostate cancer and/or colorectal cancer or a susceptibility to prostate cancer and/or colorectal cancer, by detecting particular alleles at genetic markers that appear more frequently in prostate cancer and/or colorectal cancer subjects or subjects who are susceptible to prostate cancer and/or colorectal cancer. In a particular embodiment, the invention is a method of diagnosing a susceptibility to prostate cancer and/or colorectal cancer by detecting at least one allele of at least one polymorphic marker (e.g., the markers described herein). The present invention describes methods whereby detection of particular alleles of particular markers or haplotypes is indicative of a susceptibility to prostate cancer and/or colorectal cancer. Such prognostic or predictive assays can also be used to determine prophylactic treatment of a subject prior to the onset of symptoms of prostate cancer and/or colorectal cancer.

The present invention pertains in some embodiments to methods of clinical applications of diagnosis, e.g., diagnosis performed by a medical professional. In other embodiments, the invention pertains to methods of diagnosis performed by a layman. The layman can be the customer of a genotyping service. The layman may also be a genotype service provider, who performs genotype analysis on a DNA sample from an individual, in order to provide service related to genetic risk factors for particular traits or diseases, based on the genotype status of the individual (i.e., the customer). Recent technological advances in genotyping technologies, including high-throughput genotyping of SNP markers, such as Molecular Inversion Probe array technology (e.g., Affymetrix GeneChip), and BeadArray Technologies (e.g., Illumina GoldenGate and Infinium assays) have made it possible for individuals to have their own genome assessed for up to one million SNPs simultaneously, at relatively little cost. The resulting genotype information, made available to the customer can be compared to information from the public literature about disease or trait risk associated with various SNPs. The diagnostic application of disease-associated alleles as described herein, can thus be performed either by the individual, through analysis of his/her genotype data, or by a health professional based on results of a clinical test. In other words, the diagnosis or assessment of a susceptibility based on genetic risk can be made by health professionals, genetic counselors or by the layman, based on information about his/her genotype and publications on various risk factors. In the present context, the term "diagnosing", and "diagnose a susceptibility", is meant to refer to any available diagnostic method, including those mentioned above.

In certain embodiments, a sample containing genomic DNA from an individual is collected. Such sample can for example be a buccal swab, a saliva sample, a blood sample, or other suitable samples containing genomic DNA, as described further herein. The genomic DNA is then analyzed using any common technique available to the skilled person, such as high-throughput array technologies. Results from such genotyping are stored in a convenient data storage unit, such as a data carrier, including computer databases, data storage disks, or by other convenient data storage means. In certain embodiments, the computer database is an object database, a relational database or a post-relational database. The genotype data is subsequently analyzed for the presence of certain variants known to be susceptibility variants for a particular human conditions, such as the genetic variants described herein. Genotype data can be retrieved from the data storage unit using any convenient data query method. Calculating risk conferred by a particular genotype for the individual can be based on comparing the genotype of the individual to previously determined risk (expressed as a relative risk (RR) or and odds ratio (OR), for example) for the genotype, for example for an heterozygous carrier of an at-risk variant for a particular disease or trait (such as prostate cancer and colorectal cancer). The calculated risk for the individual can be the relative risk for a person, or for a specific genotype of a person, compared to the average population with matched gender and ethnicity. The average population risk can be expressed as a weighted average of the risks of different genotypes, using results from a reference population, and the appropriate calculations to calculate the risk of a genotype group relative to the population can then be performed. Alternatively, the risk for an individual is based on a comparison of particular genotypes, for example heterozygous carriers of an at-risk allele of a marker compared with non-carriers of the at-risk allele. Using the population average may in certain embodiments be more convenient, since it provides a measure which is easy to interpret for the user, i.e. a measure that gives the risk for the individual, based on his/her genotype, compared with the average in the population. The calculated risk estimated can be made available to the customer via a website, preferably a secure website.

In certain embodiments, a service provider will include in the provided service all of the steps of isolating genomic DNA from a sample provided by the customer, performing geno-

typing of the isolated DNA, calculating genetic risk based on the genotype data, and report the risk to the customer. In some other embodiments, the service provider will include in the service the interpretation of genotype data for the individual, i.e., risk estimates for particular genetic variants based on the genotype data for the individual. In some other embodiments, the service provider may include service that includes genotyping service and interpretation of the genotype data, starting from a sample of isolated DNA from the individual (the customer).

Custom sequencing service can also be used to assess genotype status of individuals. Targeted sequencing or whole genome sequencing technologies can be used to determine the identity of nucleotides at certain polymorphic sites. Determination of such identity defines the allelic status of the individual at the site, i.e. provides genotype information. Such sequencing services can thus also be utilized to realize the present invention. As whole-genome sequencing technologies become economically feasible on a large scale, utilization of genotype information based on such technologies may become preferable. Certain embodiments of the invention encompass genotyping performed by such sequencing technologies.

In addition, in certain other embodiments, the present invention pertains to methods of diagnosing, or aiding in the diagnosis of, a decreased susceptibility to prostate cancer and/or colorectal cancer, by detecting particular genetic marker alleles or haplotypes that appear less frequently in prostate cancer and/or colorectal cancer patients than in individual not diagnosed with prostate cancer and/or colorectal cancer or in the general population.

Overall risk for multiple risk variants can be performed using standard methodology. For example, assuming a multiplicative model, i.e. assuming that the risk of individual risk variants multiply to establish the overall effect, allows for a straight-forward calculation of the overall risk for multiple markers.

As described and exemplified herein, particular marker alleles or haplotypes (e.g. the markers and haplotypes as listed in Tables 1-6) are associated with prostate cancer and colorectal cancer. In one embodiment, the marker allele or haplotype is one that confers a significant risk or susceptibility to prostate cancer and/or colorectal cancer. In another embodiment, the invention relates to a method of determining or diagnosing a susceptibility to prostate cancer and/or colorectal cancer in a human individual, the method comprising determining the presence or absence of at least one allele of at least one polymorphic marker in a nucleic acid sample obtained from the individual, wherein the at least one polymorphic marker is selected from the group consisting of the polymorphic markers listed in Table 5 and 6, and markers in linkage disequilibrium (e.g., defined as $r^2>0.2$) therewith. In another embodiment, the invention pertains to methods of diagnosing or determining a susceptibility to prostate cancer and/or colorectal cancer in a human individual, by screening for at least one marker allele as listed in Table 3 and Table 4 or markers in linkage disequilibrium therewith. In another embodiment, the invention relates to methods of diagnosing or determining a susceptibility to colorectal cancer in a human individual, by screening for at least one marker as listed in Table 4. In another embodiment, the marker allele or haplotype is more frequently present in a subject having, or who is susceptible to, prostate cancer and/or colorectal cancer (affected), as compared to the frequency of its presence in a healthy subject (control, such as population controls). In certain embodiments, the significance of association of the at least one marker allele or haplotype is characterized by a p value <0.05. In other embodiments, the significance of association is characterized by smaller p-values, such as <0.01, <0.001, <0.0001, <0.00001, <0.000001, <0.0000001, <0.00000001 or <0.000000001.

In these embodiments, the presence of the at least one marker allele or haplotype is indicative of a susceptibility to prostate cancer and/or colorectal cancer. These diagnostic methods involve detecting the presence or absence of at least one marker allele or haplotype that is associated with prostate cancer and/or colorectal cancer. The haplotypes described herein include combinations of alleles at various genetic markers (e.g., SNPs, microsatellites). The detection of the particular genetic marker alleles that make up the particular haplotypes can be performed by a variety of methods described herein and/or known in the art. For example, genetic markers can be detected at the nucleic acid level (e.g., by direct nucleotide sequencing or by other means known to the skilled in the art) or at the amino acid level if the genetic marker affects the coding sequence of a protein encoded by a cancer (prostate cancer or colorectal cancer)-associated nucleic acid (e.g., by protein sequencing or by immunoassays using antibodies that recognize such a protein). The marker alleles or haplotypes of the present invention correspond to fragments of a genomic DNA sequence associated with prostate cancer and/or colorectal cancer. Such fragments encompass the DNA sequence of the polymorphic marker or haplotype in question, but may also include DNA segments in strong LD (linkage disequilibrium) with the marker or haplotype. In one embodiment, such segments comprises segments in LD with the marker or haplotype as determined by a value of r^2 greater than 0.1 and/or $|D'|>0.8$).

In one embodiment, diagnosis of a susceptibility to prostate cancer and/or colorectal cancer can be accomplished using hybridization methods, such as Southern analysis, Northern analysis, and/or in situ hybridizations (see Current Protocols in Molecular Biology, Ausubel, F. et al., eds., John Wiley & Sons, including all supplements). The presence of a specific marker allele can be indicated by sequence-specific hybridization of a nucleic acid probe specific for the particular allele. The presence of more than specific marker allele or a specific haplotype can be indicated by using several sequence-specific nucleic acid probes, each being specific for a particular allele. In one embodiment, a haplotype can be indicated by a single nucleic acid probe that is specific for the specific haplotype (i.e., hybridizes specifically to a DNA strand comprising the specific marker alleles characteristic of the haplotype). A sequence-specific probe can be directed to hybridize to genomic DNA, RNA, or cDNA. A "nucleic acid probe", as used herein, can be a DNA probe or an RNA probe that hybridizes to a complementary sequence. One of skill in the art would know how to design such a probe so that sequence specific hybridization will occur only if a particular allele is present in a genomic sequence from a test sample.

To diagnose a susceptibility to prostate cancer and/or colorectal cancer, a hybridization sample is formed by contacting the test sample containing a prostate cancer and/or colorectal cancer-associated nucleic acid, such as a genomic DNA sample, with at least one nucleic acid probe. A non-limiting example of a probe for detecting mRNA or genomic DNA is a labeled nucleic acid probe that is capable of hybridizing to mRNA or genomic DNA sequences described herein. The nucleic acid probe can be, for example, a full-length nucleic acid molecule, or a portion thereof, such as an oligonucleotide of at least 15, 30, 50, 100, 250 or 500 nucleotides in length that is sufficient to specifically hybridize under stringent conditions to appropriate mRNA or genomic DNA. For example, the nucleic acid probe can comprise all or a

portion of the nucleotide sequence of LD Block C06 or LD Block C11, as described herein, optionally comprising at least one allele of a marker described herein, or the probe can be the complementary sequence of such a sequence. In a particular embodiment, the nucleic acid probe is a portion of the nucleotide sequence of LD Block C06 or LD Block C11, as described herein, optionally comprising at least one allele of a marker described herein, or at least one allele of one polymorphic marker or haplotype comprising at least one polymorphic marker described herein, or the probe can be the complementary sequence of such a sequence. Other suitable probes for use in the diagnostic assays of the invention are described herein. Hybridization can be performed by methods well known to the person skilled in the art (see, e.g., Current Protocols in Molecular Biology, Ausubel, F. et al., eds., John Wiley & Sons, including all supplements). In one embodiment, hybridization refers to specific hybridization, i.e., hybridization with no mismatches (exact hybridization). In one embodiment, the hybridization conditions for specific hybridization are high stringency.

Specific hybridization, if present, is detected using standard methods. If specific hybridization occurs between the nucleic acid probe and the nucleic acid in the test sample, then the sample contains the allele that is complementary to the nucleotide that is present in the nucleic acid probe. The process can be repeated for any markers of the present invention, or markers that make up a haplotype of the present invention, or multiple probes can be used concurrently to detect more than one, marker alleles at a time. It is also possible to design a single probe containing more than one marker alleles of a particular haplotype (e.g., a probe containing alleles complementary to 2, 3, 4, 5 or all of the markers that make up a particular haplotype). Detection of the particular markers of the haplotype in the sample is indicative that the source of the sample has the particular haplotype (e.g., a haplotype) and therefore is susceptible to prostate cancer and/or colorectal cancer.

In one preferred embodiment, a method utilizing a detection oligonucleotide probe comprising a fluorescent moiety or group at its 3' terminus and a quencher at its 5' terminus, and an enhancer oligonucleotide, is employed, as described by Kutyavin et al. (*Nucleic Acid Res.* 34:e128 (2006)). The fluorescent moiety can be Gig Harbor Green or Yakima Yellow, or other suitable fluorescent moieties. The detection probe is designed to hybridize to a short nucleotide sequence that includes the SNP polymorphism to be detected. Preferably, the SNP is anywhere from the terminal residue to −6 residues from the 3' end of the detection probe. The enhancer is a short oligonucleotide probe which hybridizes to the DNA template 3' relative to the detection probe. The probes are designed such that a single nucleotide gap exists between the detection probe and the enhancer nucleotide probe when both are bound to the template. The gap creates a synthetic abasic site that is recognized by an endonuclease, such as Endonuclease IV. The enzyme cleaves the dye off the fully complementary detection probe, but cannot cleave a detection probe containing a mismatch. Thus, by measuring the fluorescence of the released fluorescent moiety, assessment of the presence of a particular allele defined by nucleotide sequence of the detection probe can be performed.

The detection probe can be of any suitable size, although preferably the probe is relatively short. In one embodiment, the probe is from 5-100 nucleotides in length. In another embodiment, the probe is from 10-50 nucleotides in length, and in another embodiment, the probe is from 12-30 nucleotides in length. Other lengths of the probe are possible and within scope of the skill of the average person skilled in the art.

In a preferred embodiment, the DNA template containing the SNP polymorphism is amplified by Polymerase Chain Reaction (PCR) prior to detection. In such an embodiment, the amplified DNA serves as the template for the detection probe and the enhancer probe.

Certain embodiments of the detection probe, the enhancer probe, and/or the primers used for amplification of the template by PCR include the use of modified bases, including modified A and modified G. The use of modified bases can be useful for adjusting the melting temperature of the nucleotide molecule (probe and/or primer) to the template DNA, for example for increasing the melting temperature in regions containing a low percentage of G or C bases, in which modified A with the capability of forming three hydrogen bonds to its complementary T can be used, or for decreasing the melting temperature in regions containing a high percentage of G or C bases, for example by using modified G bases that form only two hydrogen bonds to their complementary C base in a double stranded DNA molecule. In a preferred embodiment, modified bases are used in the design of the detection nucleotide probe. Any modified base known to the skilled person can be selected in these methods, and the selection of suitable bases is well within the scope of the skilled person based on the teachings herein and known bases available from commercial sources as known to the skilled person.

In another hybridization method, Northern analysis (see Current Protocols in Molecular Biology, Ausubel, F. et al., eds., John Wiley & Sons, supra) is used to identify the presence of a polymorphism associated with prostate cancer and/or colorectal cancer. For Northern analysis, a test sample of RNA is obtained from the subject by appropriate means. As described herein, specific hybridization of a nucleic acid probe to RNA from the subject is indicative of a particular allele complementary to the probe. For representative examples of use of nucleic acid probes, see, for example, U.S. Pat. Nos. 5,288,611 and 4,851,330.

Additionally, or alternatively, a peptide nucleic acid (PNA) probe can be used in addition to, or instead of, a nucleic acid probe in the hybridization methods described herein. A PNA is a DNA mimic having a peptide-like, inorganic backbone, such as N-(2-aminoethyl)glycine units, with an organic base (A, G, C, T or U) attached to the glycine nitrogen via a methylene carbonyl linker (see, for example, Nielsen, P., et al., *Bioconjug. Chem.* 5:3-7 (1994)). The PNA probe can be designed to specifically hybridize to a molecule in a sample suspected of containing one or more of the marker alleles or haplotypes that are associated with prostate cancer and/or colorectal cancer. Hybridization of the PNA probe is thus diagnostic for prostate cancer and/or colorectal cancer or a susceptibility to prostate cancer and/or colorectal cancer

In one embodiment of the invention, a test sample containing genomic DNA obtained from the subject is collected and the polymerase chain reaction (PCR) is used to amplify a fragment comprising one or more markers or haplotypes of the present invention. As described herein, identification of a particular marker allele or haplotype associated with prostate cancer and/or colorectal cancer, can be accomplished using a variety of methods (e.g., sequence analysis, analysis by restriction digestion, specific hybridization, single stranded conformation polymorphism assays (SSCP), electrophoretic analysis, etc.). In another embodiment, diagnosis is accomplished by expression analysis using quantitative PCR (kinetic thermal cycling). This technique can, for example, utilize commercially available technologies, such as TaqMan®

(Applied Biosystems, Foster City, Calif.). The technique can assess the presence of an alteration in the expression or composition of a polypeptide or splicing variant(s) that is encoded by a nucleic acid associated with prostate cancer and/or colorectal cancer. Further, the expression of the variant(s) can be quantified as physically or functionally different.

In another embodiment of the methods of the invention, analysis by restriction digestion can be used to detect a particular allele if the allele results in the creation or elimination of a restriction site relative to a reference sequence. Restriction fragment length polymorphism (RFLP) analysis can be conducted, e.g., as described in Current Protocols in Molecular Biology, supra. The digestion pattern of the relevant DNA fragment indicates the presence or absence of the particular allele in the sample.

Sequence analysis can also be used to detect specific alleles or haplotypes associated with prostate cancer and/or colorectal cancer (e.g. the polymorphic markers of Tables 4 and 5, and markers in linkage disequilibrium therewith). Therefore, in one embodiment, determination of the presence or absence of a particular marker alleles or haplotypes comprises sequence analysis of a test sample of DNA or RNA obtained from a subject or individual. PCR or other appropriate methods can be used to amplify a portion of a nucleic acid associated with prostate cancer and/or colorectal cancer, and the presence of a specific allele can then be detected directly by sequencing the polymorphic site (or multiple polymorphic sites in a haplotype) of the genomic DNA in the sample.

Allele-specific oligonucleotides can also be used to detect the presence of a particular allele in a nucleic acid associated with prostate cancer and/or colorectal cancer (e.g. the polymorphic markers of Tables 3 and 4, and markers in linkage disequilibrium therewith), through the use of dot-blot hybridization of amplified oligonucleotides with allele-specific oligonucleotide (ASO) probes (see, for example, Saiki, R. et al., *Nature,* 324:163-166 (1986)). An "allele-specific oligonucleotide" (also referred to herein as an "allele-specific oligonucleotide probe") is an oligonucleotide of approximately 10-50 base pairs or approximately 15-30 base pairs, that specifically hybridizes to a nucleic acid associated with prostate cancer and/or colorectal cancer, and which contains a specific allele at a polymorphic site (e.g., a marker or haplotype as described herein). An allele-specific oligonucleotide probe that is specific for one or more particular a nucleic acid associated with prostate cancer and/or colorectal cancer can be prepared using standard methods (see, e.g., Current Protocols in Molecular Biology, supra). PCR can be used to amplify the desired region. The DNA containing the amplified region can be dot-blotted using standard methods (see, e.g., Current Protocols in Molecular Biology, supra), and the blot can be contacted with the oligonucleotide probe. The presence of specific hybridization of the probe to the amplified region can then be detected. Specific hybridization of an allele-specific oligonucleotide probe to DNA from the subject is indicative of a specific allele at a polymorphic site associated with DISEASE (see, e.g., Gibbs, R. et al., *Nucleic Acids Res.,* 17:2437-2448 (1989) and WO 93/22456).

In another embodiment, arrays of oligonucleotide probes that are complementary to target nucleic acid sequence segments from a subject, can be used to identify particular alleles at polymorphic sites. For example, an oligonucleotide array can be used. Oligonucleotide arrays typically comprise a plurality of different oligonucleotide probes that are coupled to a surface of a substrate in different known locations. These arrays can generally be produced using mechanical synthesis methods or light directed synthesis methods that incorporate a combination of photolithographic methods and solid phase oligonucleotide synthesis methods, or by other methods known to the person skilled in the art (see, e.g., Bier, F. F., et al. *Adv Biochem Eng Biotechnol* 109:433-53 (2008); Hoheisel, J. D., *Nat Rev Genet.* 7:200-10 (2006); Fan, J. B., et al. *Methods Enzymol* 410:57-73 (2006); Raqoussis, J. & Elvidge, G., *Expert Rev Mol Diagn* 6:145-52 (2006); Mockler, T. C., et al *Genomics* 85:1-15 (2005), and references cited therein, the entire teachings of each of which are incorporated by reference herein). Many additional descriptions of the preparation and use of oligonucleotide arrays for detection of polymorphisms can be found, for example, in U.S. Pat. No. 6,858,394, U.S. Pat. No. 6,429,027, U.S. Pat. No. 5,445,934, U.S. Pat. No. 5,700,637, U.S. Pat. No. 5,744,305, U.S. Pat. No. 5,945,334, U.S. Pat. No. 6,054,270, U.S. Pat. No. 6,300,063, U.S. Pat. No. 6,733,977, U.S. Pat. No. 7,364,858, EP 619 321, and EP 373 203, the entire teachings of which are incorporated by reference herein.

Other methods of nucleic acid analysis that are available to those skilled in the art can be used to detect a particular allele at a polymorphic site associated with prostate cancer and/or colorectal cancer (e.g. the polymorphic markers of Tables 3 and 4, and markers in linkage disequilibrium therewith). Representative methods include, for example, direct manual sequencing (Church and Gilbert, *Proc. Natl. Acad. Sci. USA,* 81: 1991-1995 (1988); Sanger, F., et al., *Proc. Natl. Acad. Sci. USA,* 74:5463-5467 (1977); Beavis, et al., U.S. Pat. No. 5,288,644); automated fluorescent sequencing; single-stranded conformation polymorphism assays (SSCP); clamped denaturing gel electrophoresis (CDGE); denaturing gradient gel electrophoresis (DGGE) (Sheffield, V., et al., *Proc. Natl. Acad. Sci. USA,* 86:232-236 (1989)), mobility shift analysis (Orita, M., et al., *Proc. Natl. Acad. Sci. USA,* 86:2766-2770 (1989)), restriction enzyme analysis (Flavell, R., et al., *Cell,* 15:25-41 (1978); Geever, R., et al., *Proc. Natl. Acad. Sci. USA,* 78:5081-5085 (1981)); heteroduplex analysis; chemical mismatch cleavage (CMC) (Cotton, R., et al., *Proc. Natl. Acad. Sci. USA,* 85:4397-4401 (1985)); RNase protection assays (Myers, R., et al., *Science,* 230:1242-1246 (1985); use of polypeptides that recognize nucleotide mismatches, such as *E. coli* mutS protein; and allele-specific PCR.

In another embodiment of the invention, diagnosis of prostate cancer and/or colorectal cancer or a susceptibility to prostate cancer and/or colorectal cancer can be made by examining expression and/or composition of a polypeptide encoded by a nucleic acid associated with prostate cancer and/or colorectal cancer in those instances where the genetic marker(s) or haplotype(s) of the present invention result in a change in the composition or expression of the polypeptide. Thus, diagnosis of a susceptibility to prostate cancer and/or colorectal cancer can be made by examining expression and/or composition of one of these polypeptides, or another polypeptide encoded by a nucleic acid associated with prostate cancer and/or colorectal cancer, in those instances where the genetic marker or haplotype of the present invention results in a change in the composition or expression of the polypeptide. The haplotypes and markers of the present invention that show association to prostate cancer and/or colorectal cancer may play a role through their effect on one or more of these nearby genes. Possible mechanisms affecting these genes include, e.g., effects on transcription, effects on RNA splicing, alterations in relative amounts of alternative splice forms of mRNA, effects on RNA stability, effects on transport from the nucleus to cytoplasm, and effects on the efficiency and accuracy of translation.

Thus, in another embodiment, the variants (markers or haplotypes) of the invention showing association to prostate

cancer and/or colorectal cancer affect the expression of a nearby gene. It is well known that regulatory element affecting gene expression may be located far away, even as far as tenths or hundreds of kilobases away, from the promoter region of a gene. By assaying for the presence or absence of at least one allele of at least one polymorphic marker of the present invention, it is thus possible to assess the expression level of such nearby genes.

A variety of methods can be used for detecting protein expression levels, including enzyme linked immunosorbent assays (ELISA), Western blots, immunoprecipitations and immunofluorescence. A test sample from a subject is assessed for the presence of an alteration in the expression and/or an alteration in composition of the polypeptide encoded by a nucleic acid associated with prostate cancer and/or colorectal cancer. An alteration in expression of a polypeptide encoded by a nucleic acid associated with prostate cancer and/or colorectal cancer can be, for example, an alteration in the quantitative polypeptide expression (i.e., the amount of polypeptide produced). An alteration in the composition of a polypeptide encoded by a nucleic acid associated with prostate cancer and/or colorectal cancer is an alteration in the qualitative polypeptide expression (e.g., expression of a mutant polypeptide or of a different splicing variant). In one embodiment, diagnosis of a susceptibility to prostate cancer and/or colorectal cancer is made by detecting a particular splicing variant encoded by a nucleic acid associated with prostate cancer and/or colorectal cancer, or a particular pattern of splicing variants.

Both such alterations (quantitative and qualitative) can also be present. An "alteration" in the polypeptide expression or composition, as used herein, refers to an alteration in expression or composition in a test sample, as compared to the expression or composition of the polypeptide in a control sample. A control sample is a sample that corresponds to the test sample (e.g., is from the same type of cells), and is from a subject who is not affected by, and/or who does not have a susceptibility to, prostate cancer and/or colorectal cancer. In one embodiment, the control sample is from a subject that does not possess a marker allele or haplotype as described herein. Similarly, the presence of one or more different splicing variants in the test sample, or the presence of significantly different amounts of different splicing variants in the test sample, as compared with the control sample, can be indicative of a susceptibility to prostate cancer and/or colorectal cancer. An alteration in the expression or composition of the polypeptide in the test sample, as compared with the control sample, can be indicative of a specific allele in the instance where the allele alters a splice site relative to the reference in the control sample. Various means of examining expression or composition of a polypeptide encoded by a nucleic acid are known to the person skilled in the art and can be used, including spectroscopy, colorimetry, electrophoresis, isoelectric focusing, and immunoassays (e.g., David et al., U.S. Pat. No. 4,376,110) such as immunoblotting (see, e.g., Current Protocols in Molecular Biology, particularly chapter 10, supra).

For example, in one embodiment, an antibody (e.g., an antibody with a detectable label) that is capable of binding to a polypeptide encoded by a nucleic acid associated with prostate cancer and/or colorectal cancer can be used. Antibodies can be polyclonal or monoclonal. An intact antibody, or a fragment thereof (e.g., Fv, Fab, Fab', $F(ab')_2$) can be used. The term "labeled", with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (i.e., physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a labeled secondary antibody (e.g., a fluorescently-labeled secondary antibody) and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently-labeled streptavidin.

In one embodiment of this method, the level or amount of polypeptide encoded by a nucleic acid associated with prostate cancer and/or colorectal cancer in a test sample is compared with the level or amount of the polypeptide in a control sample. A level or amount of the polypeptide in the test sample that is higher or lower than the level or amount of the polypeptide in the control sample, such that the difference is statistically significant, is indicative of an alteration in the expression of the polypeptide encoded by the nucleic acid, and is diagnostic for a particular allele or haplotype responsible for causing the difference in expression. Alternatively, the composition of the polypeptide in a test sample is compared with the composition of the polypeptide in a control sample. In another embodiment, both the level or amount and the composition of the polypeptide can be assessed in the test sample and in the control sample.

In another embodiment, the diagnosis of a susceptibility to prostate cancer and/or colorectal cancer is made by detecting at least one marker or haplotypes of the present invention (e.g., associated alleles of the markers listed in Tables 1-6, and markers in linkage disequilibrium therewith), in combination with an additional protein-based, RNA-based or DNA-based assay. The methods of the invention can also be used in combination with an analysis of a subject's family history and risk factors (e.g., environmental risk factors, lifestyle risk factors).

Kits

Kits useful in the methods of the invention comprise components useful in any of the methods described herein, including for example, primers for nucleic acid amplification, hybridization probes, restriction enzymes (e.g., for RFLP analysis), allele-specific oligonucleotides, antibodies that bind to an altered polypeptide encoded by a nucleic acid of the invention as described herein (e.g., a genomic segment comprising at least one polymorphic marker and/or haplotype of the present invention) or to a non-altered (native) polypeptide encoded by a nucleic acid of the invention as described herein, means for amplification of a nucleic acid associated with prostate cancer and/or colorectal cancer, means for analyzing the nucleic acid sequence of a nucleic acid associated with prostate cancer and/or colorectal cancer, means for analyzing the amino acid sequence of a polypeptide encoded by a nucleic acid associated with prostate cancer and/or colorectal cancer (e.g., a prostate cancer and/or colorectal cancer protein encoded by a prostate cancer and/or colorectal cancer-associated gene), etc. The kits can for example include necessary buffers, nucleic acid primers for amplifying nucleic acids of the invention (e.g., a nucleic acid segment comprising one or more of the polymorphic markers as described herein), and reagents for allele-specific detection of the fragments amplified using such primers and necessary enzymes (e.g., DNA polymerase). Additionally, kits can provide reagents for assays to be used in combination with the methods of the present invention, e.g., reagents for use with other prostate cancer and/or colorectal cancer diagnostic assays.

In one embodiment, the invention is a kit for assaying a sample from a subject to detect the presence of prostate cancer and/or colorectal cancer, symptoms associated with prostate cancer and/or colorectal cancer, or a susceptibility to prostate cancer and/or colorectal cancer in a subject, wherein the kit comprises reagents necessary for selectively detecting at least one allele of at least one polymorphism of the present

invention in the genome of the individual. In a particular embodiment, the reagents comprise at least one contiguous oligonucleotide that hybridizes to a fragment of the genome of the individual comprising at least one polymorphism of the present invention. In another embodiment, the reagents comprise at least one pair of oligonucleotides that hybridize to opposite strands of a genomic segment obtained from a subject, wherein each oligonucleotide primer pair is designed to selectively amplify a fragment of the genome of the individual that includes at least one polymorphism, wherein the polymorphism is selected from the group consisting of the polymorphisms as listed in Tables 1-6, and polymorphic markers in linkage disequilibrium therewith. In yet another embodiment the fragment is at least 20 base pairs in size. Such oligonucleotides or nucleic acids (e.g., oligonucleotide primers) can be designed using portions of the nucleic acid sequence flanking polymorphisms (e.g., SNPs or microsatellites) that are indicative of prostate cancer and/or colorectal cancer. In another embodiment, the kit comprises one or more labeled nucleic acids capable of allele-specific detection of one or more specific polymorphic markers or haplotypes associated with prostate cancer and/or colorectal cancer, and reagents for detection of the label. Suitable labels include, e.g., a radioisotope, a fluorescent label, an enzyme label, an enzyme co-factor label, a magnetic label, a spin label, an epitope label.

In particular embodiments, the polymorphic marker or haplotype to be detected by the reagents of the kit comprises one or more markers, two or more markers, three or more markers, four or more markers or five or more markers selected from the group consisting of the markers set forth in Tables 1-6. In another embodiment, the marker or haplotype to be detected comprises the markers set forth in Tables 3 and 4. In another embodiment, the marker or haplotype to be detected comprises at least one marker from the group of markers in strong linkage disequilibrium, as defined by values of r^2 greater than 0.2, to at least one of the group of markers listed in Tables 3 and 4. In another embodiment, the marker or haplotype to be detected is selected from the group consisting of rs10896450, rs7947353, rs11228565 and rs10943605.

In one preferred embodiment, the kit for detecting the markers of the invention comprises a detection oligonucleotide probe, that hybridizes to a segment of template DNA containing a SNP polymorphisms to be detected, an enhancer oligonucleotide probe and an endonuclease. As explained in the above, the detection oligonucleotide probe comprises a fluorescent moiety or group at its 3' terminus and a quencher at its 5' terminus, and an enhancer oligonucleotide, is employed, as described by Kutyavin et al. (*Nucleic Acid Res.* 34:e128 (2006)). The fluorescent moiety can be Gig Harbor Green or Yakima Yellow, or other suitable fluorescent moieties. The detection probe is designed to hybridize to a short nucleotide sequence that includes the SNP polymorphism to be detected. Preferably, the SNP is anywhere from the terminal residue to −6 residues from the 3' end of the detection probe. The enhancer is a short oligonucleotide probe which hybridizes to the DNA template 3' relative to the detection probe. The probes are designed such that a single nucleotide gap exists between the detection probe and the enhancer nucleotide probe when both are bound to the template. The gap creates a synthetic abasic site that is recognized by an endonuclease, such as Endonuclease IV. The enzyme cleaves the dye off the fully complementary detection probe, but cannot cleave a detection probe containing a mismatch. Thus, by measuring the fluorescence of the released fluorescent moiety, assessment of the presence of a particular allele defined by nucleotide sequence of the detection probe can be performed.

The detection probe can be of any suitable size, although preferably the probe is relatively short. In one embodiment, the probe is from 5-100 nucleotides in length. In another embodiment, the probe is from 10-50 nucleotides in length, and in another embodiment, the probe is from 12-30 nucleotides in length. Other lengths of the probe are possible and within scope of the skill of the average person skilled in the art.

In a preferred embodiment, the DNA template containing the SNP polymorphism is amplified by Polymerase Chain Reaction (PCR) prior to detection, and primers for such amplification are included in the reagent kit. In such an embodiment, the amplified DNA serves as the template for the detection probe and the enhancer probe.

Certain embodiments of the detection probe, the enhancer probe, and/or the primers used for amplification of the template by PCR include the use of modified bases, including modified A and modified G. The use of modified bases can be useful for adjusting the melting temperature of the nucleotide molecule (probe and/or primer) to the template DNA, for example for increasing the melting temperature in regions containing a low percentage of G or C bases, in which modified A with the capability of forming three hydrogen bonds to its complementary T can be used, or for decreasing the melting temperature in regions containing a high percentage of G or C bases, for example by using modified G bases that form only two hydrogen bonds to their complementary C base in a double stranded DNA molecule. In a preferred embodiment, modified bases are used in the design of the detection nucleotide probe. Any modified base known to the skilled person can be selected in these methods, and the selection of suitable bases is well within the scope of the skilled person based on the teachings herein and known bases available from commercial sources as known to the skilled person.

In one of such embodiments, determination of the presence of the marker or haplotype is indicative of a susceptibility (increased susceptibility or decreased susceptibility) to prostate cancer and/or colorectal cancer. In another embodiment, the presence of the marker or haplotype is indicative of response to a therapeutic agent for prostate cancer and/or colorectal cancer. In another embodiment, the presence of the marker or haplotype is indicative of prognosis of prostate cancer and/or colorectal cancer. In yet another embodiment, the presence of the marker or haplotype is indicative of progress of treatment of prostate cancer and/or colorectal cancer. Such treatment may include intervention by surgery, medication or by other means (e.g., lifestyle changes).

In a further aspect of the present invention, a pharmaceutical pack (kit) is provided, the pack comprising a therapeutic agent and a set of instructions for administration of the therapeutic agent to humans diagnostically tested for one or more variants of the present invention, as disclosed herein. The therapeutic agent can be a small molecule drug, an antibody, a peptide, an antisense or RNAi molecule, or other therapeutic molecules. In one embodiment, an individual identified as a carrier of at least one variant of the present invention is instructed to take a prescribed dose of the therapeutic agent. In one such embodiment, an individual identified as a homozygous carrier of at least one variant of the present invention is instructed to take a prescribed dose of the therapeutic agent. In another embodiment, an individual identified as a non-carrier of at least one variant of the present invention is instructed to take a prescribed dose of the therapeutic agent.

In certain embodiments, the kit further comprises a set of instructions for using the reagents comprising the kit. In certain embodiments, the kit further comprises a collection of data comprising correlation data between the polymorphic markers assessed by the kit and susceptibility to prostate cancer and/or colorectal cancer.

Therapeutic Agents

Variants of the present invention (e.g., the markers of the invention, e.g., the markers listed in Tables 1-6, e.g., the markers set forth in Tables 3 and 4, and markers in linkage disequilibrium therewith, e.g., rs10896450, rs7947353, rs11228565 and rs10943605) can be used to identify novel therapeutic targets for prostate cancer and/or colorectal cancer. For example, genes containing, or in linkage disequilibrium with, variants (markers and/or haplotypes) associated with prostate cancer and/or colorectal cancer, or their products, as well as genes or their products that are directly or indirectly regulated by or interact with these variant genes or their products, can be targeted for the development of therapeutic agents to treat prostate cancer and/or colorectal cancer, or prevent or delay onset of symptoms associated with prostate cancer and/or colorectal cancer. Therapeutic agents may comprise one or more of, for example, small non-protein and non-nucleic acid molecules, proteins, peptides, protein fragments, nucleic acids (DNA, RNA), PNA (peptide nucleic acids), or their derivatives or mimetics which can modulate the function and/or levels of the target genes or their gene products.

The nucleic acids and/or variants of the invention, or nucleic acids comprising their complementary sequence, may be used as antisense constructs to control gene expression in cells, tissues or organs. The methodology associated with antisense techniques is well known to the skilled artisan, and is described and reviewed in *Antisense Drug Technology: Principles, Strategies, and Applications*, Crooke, ed., Marcel Dekker Inc., New York (2001). In general, antisense agents (antisense oligonucleotides) are comprised of single stranded oligonucleotides (RNA or DNA) that are capable of binding to a complimentary nucleotide segment. By binding the appropriate target sequence, an RNA-RNA, DNA-DNA or RNA-DNA duplex is formed. The antisense oligonucleotides are complementary to the sense or coding strand of a gene. It is also possible to form a triple helix, where the antisense oligonucleotide binds to duplex DNA.

Several classes of antisense oligonucleotide are known to those skilled in the art, including cleavers and blockers. The former bind to target RNA sites, activate intracellular nucleases (e.g., RnaseH or Rnase L), that cleave the target RNA. Blockers bind to target RNA, inhibit protein translation by steric hindrance of the ribosomes. Examples of blockers include nucleic acids, morpholino compounds, locked nucleic acids and methylphosphonates (Thompson, *Drug Discovery Today,* 7:912-917 (2002)). Antisense oligonucleotides are useful directly as therapeutic agents, and are also useful for determining and validating gene function, for example by gene knock-out or gene knock-down experiments. Antisense technology is further described in Layery et al., *Curr. Opin. Drug Discov. Devel.* 6:561-569 (2003), Stephens et al., *Curr. Opin. Mol. Ther.* 5:118-122 (2003), Kurreck, *Eur. J. Biochem.* 270:1628-44 (2003), Dias et al., *Mol. Cancer. Ter.* 1:347-55 (2002), Chen, *Methods Mol. Med.* 75:621-636 (2003), Wang et al., *Curr. Cancer Drug Targets* 1:177-96 (2001), and Bennett, *Antisense Nucleic Acid Drug. Dev.* 12:215-24 (2002).

In certain embodiments, the antisense agent is an oligonucleotide that is capable of binding to a nucleotide segment of the LD Block C11 or LD Block C06, as described herein. Antisense nucleotides can be from 5-500 nucleotides in length, including 5-200 nucleotides, 5-100 nucleotides, 8-50 nucleotides, and 8-30 nucleotides. In certain preferred embodiments, the antisense nucleotides is from 14-50 nucleotides in length, including 14-40 nucleotides and 14-30 nucleotides. In certain such embodiments, the antisense nucleotide is capable of binding to a nucleotide segment of LD Block C11 as set forth in SEQ ID NO:201.

The variants described herein can be used for the selection and design of antisense reagents that are specific for particular variants. Using information about the variants described herein, antisense oligonucleotides or other antisense molecules that specifically target mRNA molecules that contain one or more variants of the invention can be designed. In this manner, expression of mRNA molecules that contain one or more variant of the present invention (markers and/or haplotypes) can be inhibited or blocked. In one embodiment, the antisense molecules are designed to specifically bind a particular allelic form (i.e., one or several variants (alleles and/or haplotypes)) of the target nucleic acid, thereby inhibiting translation of a product originating from this specific allele or haplotype, but which do not bind other or alternate variants at the specific polymorphic sites of the target nucleic acid molecule.

As antisense molecules can be used to inactivate mRNA so as to inhibit gene expression, and thus protein expression, the molecules can be used to treat a disease or disorder, including prostate cancer and/or colorectal cancer. The methodology can involve cleavage by means of ribozymes containing nucleotide sequences complementary to one or more regions in the mRNA that attenuate the ability of the mRNA to be translated. Such mRNA regions include, for example, protein-coding regions, in particular protein-coding regions corresponding to catalytic activity, substrate and/or ligand binding sites, or other functional domains of a protein.

The phenomenon of RNA interference (RNAi) has been actively studied for the last decade, since its original discovery in *C. elegans* (Fire et al., *Nature* 391:806-11 (1998)), and in recent years its potential use in treatment of human disease has been actively pursued (reviewed in Kim & Rossi, *Nature Rev. Genet.* 8:173-204 (2007)). RNA interference (RNAi), also called gene silencing, is based on using double-stranded RNA molecules (dsRNA) to turn off specific genes. In the cell, cytoplasmic double-stranded RNA molecules (dsRNA) are processed by cellular complexes into small interfering RNA (siRNA). The siRNA guide the targeting of a protein-RNA complex to specific sites on a target mRNA, leading to cleavage of the mRNA (Thompson, *Drug Discovery Today,* 7:912-917 (2002)). The siRNA molecules are typically about 20, 21, 22 or 23 nucleotides in length. Thus, one aspect of the invention relates to isolated nucleic acid molecules, and the use of those molecules for RNA interference, i.e. as small interfering RNA molecules (siRNA). In one embodiment, the isolated nucleic acid molecules are 18-26 nucleotides in length, preferably 19-25 nucleotides in length, more preferably 20-24 nucleotides in length, and more preferably 21, 22 or 23 nucleotides in length.

Another pathway for RNAi-mediated gene silencing originates in endogenously encoded primary microRNA (pri-miRNA) transcripts, which are processed in the cell to generate precursor miRNA (pre-miRNA). These miRNA molecules are exported from the nucleus to the cytoplasm, where they undergo processing to generate mature miRNA molecules (miRNA), which direct translational inhibition by recognizing target sites in the 3' untranslated regions of

mRNAs, and subsequent mRNA degradation by processing P-bodies (reviewed in Kim & Rossi, *Nature Rev. Genet.* 8:173-204 (2007)).

Clinical applications of RNAi include the incorporation of synthetic siRNA duplexes, which preferably are approximately 20-23 nucleotides in size, and preferably have 3' overlaps of 2 nucleotides. Knockdown of gene expression is established by sequence-specific design for the target mRNA. Several commercial sites for optimal design and synthesis of such molecules are known to those skilled in the art.

Other applications provide longer siRNA molecules (typically 25-30 nucleotides in length, preferably about 27 nucleotides), as well as small hairpin RNAs (shRNAs; typically about 29 nucleotides in length). The latter are naturally expressed, as described in Amarzguioui et al. (*FEBS Lett.* 579:5974-81 (2005)). Chemically synthetic siRNAs and shRNAs are substrates for in vivo processing, and in some cases provide more potent gene-silencing than shorter designs (Kim et al., *Nature Biotechnol.* 23:222-226 (2005); Siolas et al., *Nature Biotechnol.* 23:227-231 (2005)). In general siRNAs provide for transient silencing of gene expression, because their intracellular concentration is diluted by subsequent cell divisions. By contrast, expressed shRNAs mediate long-term, stable knockdown of target transcripts, for as long as transcription of the shRNA takes place (Marques et al., *Nature Biotechnol.* 23:559-565 (2006); Brummelkamp et al., *Science* 296: 550-553 (2002)).

Since RNAi molecules, including siRNA, miRNA and shRNA, act in a sequence-dependent manner, the variants of the present invention (e.g., the markers set forth in Tables 1-6, e.g., the markers set forth in Tables 3 and 4) can be used to design RNAi reagents that recognize specific nucleic acid molecules comprising specific alleles and/or haplotypes (e.g., the alleles and/or haplotypes of the present invention), while not recognizing nucleic acid molecules comprising other alleles or haplotypes. These RNAi reagents can thus recognize and destroy the target nucleic acid molecules. As with antisense reagents, RNAi reagents can be useful as therapeutic agents (i.e., for turning off disease-associated genes or disease-associated gene variants), but may also be useful for characterizing and validating gene function (e.g., by gene knock-out or gene knock-down experiments).

Delivery of RNAi may be performed by a range of methodologies known to those skilled in the art. Methods utilizing non-viral delivery include cholesterol, stable nucleic acid-lipid particle (SNALP), heavy-chain antibody fragment (Fab), aptamers and nanoparticles. Viral delivery methods include use of lentivirus, adenovirus and adeno-associated virus. The siRNA molecules are in some embodiments chemically modified to increase their stability. This can include modifications at the 2' position of the ribose, including 2'-O-methylpurines and 2'-fluoropyrimidines, which provide resistance to Rnase activity. Other chemical modifications are possible and known to those skilled in the art.

The following references provide a further summary of RNAi, and possibilities for targeting specific genes using RNAi: Kim & Rossi, *Nat. Rev. Genet.* 8:173-184 (2007), Chen & Rajewsky, *Nat. Rev. Genet.* 8: 93-103 (2007), Reynolds, et al., *Nat. Biotechnol.* 22:326-330 (2004), Chi et al., *Proc. Natl. Acad. Sci. USA* 100:6343-6346 (2003), Vickers et al., *J. Biol. Chem.* 278:7108-7118 (2003), Agami, *Curr. Opin. Chem. Biol.* 6:829-834 (2002), Lavery, et al., *Curr. Opin. Drug Discov. Devel.* 6:561-569 (2003), Shi, *Trends Genet.* 19:9-12 (2003), Shuey et al., *Drug Discov. Today* 7:1040-46 (2002), McManus et al., *Nat. Rev. Genet.* 3:737-747 (2002), Xia et al., *Nat. Biotechnol.* 20:1006-10 (2002), Plasterk et al., *curr. Opin. Genet. Dev.* 10:562-7 (2000), Bosher et al., *Nat. Cell Biol.* 2:E31-6 (2000), and Hunter, *Curr. Biol.* 9:R440-442 (1999).

A genetic defect leading to increased predisposition or risk for development of a disease, such as prostate cancer and/or colorectal cancer, or a defect causing the disease, may be corrected permanently by administering to a subject carrying the defect a nucleic acid fragment that incorporates a repair sequence that supplies the normal/wild-type nucleotide(s) at the site of the genetic defect. Such site-specific repair sequence may concompass an RNA/DNA oligonucleotide that operates to promote endogenous repair of a subject's genomic DNA. The administration of the repair sequence may be performed by an appropriate vehicle, such as a complex with polyethelenimine, encapsulated in anionic liposomes, a viral vector such as an adenovirus vector, or other pharmaceutical compositions suitable for promoting intracellular uptake of the administered nucleic acid. The genetic defect may then be overcome, since the chimeric oligonucleotides induce the incorporation of the normal sequence into the genome of the subject, leading to expression of the normal/wild-type gene product. The replacement is propagated, thus rendering a permanent repair and alleviation of the symptoms associated with the disease or condition.

The present invention provides methods for identifying compounds or agents that can be used to treat prostate cancer and/or colorectal cancer. Thus, the variants of the invention are useful as targets for the identification and/or development of therapeutic agents. Such methods may include assaying the ability of an agent or compound to modulate the activity and/or expression of a nucleic acid that includes at least one of the variants (markers and/or haplotypes) of the present invention, or the encoded product of the nucleic acid. This in turn can be used to identify agents or compounds that inhibit or alter the undesired activity or expression of the encoded nucleic acid product. Assays for performing such experiments can be performed in cell-based systems or in cell-free systems, as known to the skilled person. Cell-based systems include cells naturally expressing the nucleic acid molecules of interest, or recombinant cells that have been genetically modified so as to express a certain desired nucleic acid molecule.

Variant gene expression in a patient can be assessed by expression of a variant-containing nucleic acid sequence (for example, a gene containing at least one variant of the present invention, which can be transcribed into RNA containing the at least one variant, and in turn translated into protein), or by altered expression of a normal/wild-type nucleic acid sequence due to variants affecting the level or pattern of expression of the normal transcripts, for example variants in the regulatory or control region of the gene. Assays for gene expression include direct nucleic acid assays (mRNA), assays for expressed protein levels, or assays of collateral compounds involved in a pathway, for example a signal pathway. Furthermore, the expression of genes that are up- or down-regulated in response to the signal pathway can also be assayed. One embodiment includes operably linking a reporter gene, such as luciferase, to the regulatory region of the gene(s) of interest.

Modulators of gene expression can in one embodiment be identified when a cell is contacted with a candidate compound or agent, and the expression of mRNA is determined. The expression level of mRNA in the presence of the candidate compound or agent is compared to the expression level in the absence of the compound or agent. Based on this comparison, candidate compounds or agents for treating prostate cancer and/or colorectal cancer can be identified as those modulating

the gene expression of the variant gene. When expression of mRNA or the encoded protein is statistically significantly greater in the presence of the candidate compound or agent than in its absence, then the candidate compound or agent is identified as a stimulator or up-regulator of expression of the nucleic acid. When nucleic acid expression or protein level is statistically significantly less in the presence of the candidate compound or agent than in its absence, then the candidate compound is identified as an inhibitor or down-regulator of the nucleic acid expression.

The invention further provides methods of treatment using a compound identified through drug (compound and/or agent) screening as a gene modulator (i.e. stimulator and/or inhibitor of gene expression).

Methods of Assessing Probability of Response to Therapeutic Agents, Methods of Monitoring Progress of Treatment and Methods of Treatment

As is known in the art, individuals can have differential responses to a particular therapy (e.g., a therapeutic agent or therapeutic method). Pharmacogenomics addresses the issue of how genetic variations (e.g., the variants (markers and/or haplotypes) of the present invention) affect drug response, due to altered drug disposition and/or abnormal or altered action of the drug. Thus, the basis of the differential response may be genetically determined in part. Clinical outcomes due to genetic variations affecting drug response may result in toxicity of the drug in certain individuals (e.g., carriers or non-carriers of the genetic variants of the present invention), or therapeutic failure of the drug. Therefore, the variants of the present invention may determine the manner in which a therapeutic agent and/or method acts on the body, or the way in which the body metabolizes the therapeutic agent.

Accordingly, in one embodiment, the presence of a particular allele at a polymorphic site or haplotype is indicative of a different, e.g. a different response rate, to a particular treatment modality for prostate cancer and/or colorectal cancer. This means that a patient diagnosed with prostate cancer and/or colorectal cancer, and carrying a certain allele at a polymorphic or haplotype of the present invention (e.g., the at-risk and protective alleles and/or haplotypes of the invention) would respond better to, or worse to, a specific therapeutic, drug therapy and/or other therapy used to treat the disease. Therefore, the presence or absence of the marker allele or haplotype could aid in deciding what treatment should be used for a the patient. For example, for a newly diagnosed patient, the presence of a marker or haplotype of the present invention may be assessed (e.g., through testing DNA derived from a blood sample, as described herein). If the patient is positive for a marker allele or haplotype at (that is, at least one specific allele of the marker, or haplotype, is present), then the physician recommends one particular therapy, while if the patient is negative for the at least one allele of a marker, or a haplotype, then a different course of therapy may be recommended (which may include recommending that no immediate therapy, other than serial monitoring for progression of the disease, be performed). Thus, the patient's carrier status could be used to help determine whether a particular treatment modality should be administered. The value lies within the possibilities of being able to diagnose the disease at an early stage, to select the most appropriate treatment, and provide information to the clinician about prognosis/aggressiveness of the disease in order to be able to apply the most appropriate treatment.

The present invention also relates to methods of monitoring progress or effectiveness of a treatment for a prostate cancer and/or colorectal cancer. This can be done based on the genotype and/or haplotype status of the markers and haplotypes of the present invention, i.e., by assessing the absence or presence of at least one allele of at least one polymorphic marker as disclosed herein, or by monitoring expression of genes that are associated with the variants (markers and haplotypes) of the present invention. The risk gene mRNA or the encoded polypeptide can be measured in a tissue sample (e.g., a peripheral blood sample, or a biopsy sample). Expression levels and/or mRNA levels can thus be determined before and during treatment to monitor its effectiveness. Alternatively, or concomitantly, the genotype and/or haplotype status of at least one risk variant for prostate cancer and/or colorectal cancer as presented herein is determined before and during treatment to monitor its effectiveness.

Alternatively, biological networks or metabolic pathways related to the markers and haplotypes of the present invention can be monitored by determining mRNA and/or polypeptide levels. This can be done for example, by monitoring expression levels or polypeptides for several genes belonging to the network and/or pathway, in samples taken before and during treatment. Alternatively, metabolites belonging to the biological network or metabolic pathway can be determined before and during treatment. Effectiveness of the treatment is determined by comparing observed changes in expression levels/metabolite levels during treatment to corresponding data from healthy subjects.

In a further aspect, the markers of the present invention can be used to increase power and effectiveness of clinical trials. Thus, individuals who are carriers of at least one at-risk variant of the present invention, i.e. individuals who are carriers of at least one allele of at least one polymorphic marker conferring increased risk of developing prostate cancer and/or colorectal cancer may be more likely to respond to a particular treatment modality. In one embodiment, individuals who carry at-risk variants for gene(s) in a pathway and/or metabolic network for which a particular treatment (e.g., small molecule drug) is targeting, are more likely to be responders to the treatment. In another embodiment, individuals who carry at-risk variants for a gene, which expression and/or function is altered by the at-risk variant, are more likely to be responders to a treatment modality targeting that gene, its expression or its gene product. This application can improve the safety of clinical trials, but can also enhance the chance that a clinical trial will demonstrate statistically significant efficacy, which may be limited to a certain sub-group of the population. Thus, one possible outcome of such a trial is that carriers of certain genetic variants, e.g., the markers and haplotypes of the present invention, are statistically significantly likely to show positive response to the therapeutic agent, i.e. experience alleviation of symptoms associated with prostate cancer and/or colorectal cancer when taking the therapeutic agent or drug as prescribed.

In a further aspect, the markers and haplotypes of the present invention can be used for targeting the selection of pharmaceutical agents for specific individuals. Personalized selection of treatment modalities, lifestyle changes or combination of lifestyle changes and administration of particular treatment, can be realized by the utilization of the at-risk variants of the present invention. Thus, the knowledge of an individual's status for particular markers of the present invention, can be useful for selection of treatment options that target genes or gene products affected by the at-risk variants of the invention. Certain combinations of variants may be suitable for one selection of treatment options, while other gene variant combinations may target other treatment options. Such combination of variant may include one variant, two variants, three variants, or four or more variants, as

needed to determine with clinically reliable accuracy the selection of treatment module.

Computer-Implemented Aspects

As understood by those of ordinary skill in the art, the methods and information described herein may be implemented, in all or in part, as computer executable instructions on known computer readable media. For example, the methods described herein may be implemented in hardware. Alternatively, the method may be implemented in software stored in, for example, one or more memories or other computer readable medium and implemented on one or more processors. As is known, the processors may be associated with one or more controllers, calculation units and/or other units of a computer system, or implanted in firmware as desired. If implemented in software, the routines may be stored in any computer readable memory such as in RAM, ROM, flash memory, a magnetic disk, a laser disk, or other storage medium, as is also known. Likewise, this software may be delivered to a computing device via any known delivery method including, for example, over a communication channel such as a telephone line, the Internet, a wireless connection, etc., or via a transportable medium, such as a computer readable disk, flash drive, etc.

More generally, and as understood by those of ordinary skill in the art, the various steps described above may be implemented as various blocks, operations, tools, modules and techniques which, in turn, may be implemented in hardware, firmware, software, or any combination of hardware, firmware, and/or software. When implemented in hardware, some or all of the blocks, operations, techniques, etc. may be implemented in, for example, a custom integrated circuit (IC), an application specific integrated circuit (ASIC), a field programmable logic array (FPGA), a programmable logic array (PLA), etc.

When implemented in software, the software may be stored in any known computer readable medium such as on a magnetic disk, an optical disk, or other storage medium, in a RAM or ROM or flash memory of a computer, processor, hard disk drive, optical disk drive, tape drive, etc. Likewise, the software may be delivered to a user or a computing system via any known delivery method including, for example, on a computer readable disk or other transportable computer storage mechanism.

The FIGURE illustrates an example of a suitable computing system environment **100** on which a system for the steps of the claimed method and apparatus may be implemented. The computing system environment **100** is only one example of a suitable computing environment and is not intended to suggest any limitation as to the scope of use or functionality of the method or apparatus of the claims. Neither should the computing environment **100** be interpreted as having any dependency or requirement relating to any one or combination of components illustrated in the exemplary operating environment **100**.

The steps of the claimed method and system are operational with numerous other general purpose or special purpose computing system environments or configurations. Examples of well known computing systems, environments, and/or configurations that may be suitable for use with the methods or system of the claims include, but are not limited to, personal computers, server computers, hand-held or laptop devices, multiprocessor systems, microprocessor-based systems, set top boxes, programmable consumer electronics, network PCs, minicomputers, mainframe computers, distributed computing environments that include any of the above systems or devices; and the like.

The steps of the claimed method and system may be described in the general context of computer-executable instructions, such as program modules, being executed by a computer. Generally, program modules include routines, programs, objects, components, data structures, etc. that perform particular tasks or implement particular abstract data types. The methods and apparatus may also be practiced in distributed computing environments where tasks are performed by remote processing devices that are linked through a communications network. In both integrated and distributed computing environments, program modules may be located in both local and remote computer storage media including memory storage devices.

With reference to the FIGURE, an exemplary system for implementing the steps of the claimed method and system includes a general purpose computing device in the form of a computer **110**. Components of computer **110** may include, but are not limited to, a processing unit **120**, a system memory **130**, and a system bus **121** that couples various system components including the system memory to the processing unit **120**. The system bus **121** may be any of several types of bus structures including a memory bus or memory controller, a peripheral bus, and a local bus using any of a variety of bus architectures. By way of example, and not limitation, such architectures include Industry Standard Architecture (USA) bus, Micro Channel Architecture (MCA) bus, Enhanced ISA (EISA) bus, Video Electronics Standards Association (VESA) local bus, and Peripheral Component Interconnect (PCI) bus also known as Mezzanine bus.

Computer **110** typically includes a variety of computer readable media. Computer readable media can be any available media that can be accessed by computer **110** and includes both volatile and nonvolatile media, removable and non-removable media. By way of example, and not limitation, computer readable media may comprise computer storage media and communication media. Computer storage media includes both volatile and nonvolatile, removable and non-removable media implemented in any method or technology for storage of information such as computer readable instructions, data structures, program modules or other data. Computer storage media includes, but is not limited to, RAM, ROM, EEPROM, flash memory or other memory technology, CD-ROM, digital versatile disks (DVD) or other optical disk storage, magnetic cassettes, magnetic tape, magnetic disk storage or other magnetic storage devices, or any other medium which can be used to store the desired information and which can accessed by computer **110**. Communication media typically embodies computer readable instructions, data structures, program modules or other data in a modulated data signal such as a carrier wave or other transport mechanism and includes any information delivery media. The term "modulated data signal" means a signal that has one or more of its characteristics set or changed in such a manner as to encode information in the signal. By way of example, and not limitation, communication media includes wired media such as a wired network or direct-wired connection, and wireless media such as acoustic, RF, infrared and other wireless media. Combinations of the any of the above should also be included within the scope of computer readable media.

The system memory **130** includes computer storage media in the form of volatile and/or nonvolatile memory such as read only memory (ROM) **131** and random access memory (RAM) **132**. A basic input/output system **133** (BIOS), containing the basic routines that help to transfer information between elements within computer **110**, such as during start-up, is typically stored in ROM **131**. RAM **132** typically contains data and/or program modules that are immediately

accessible to and/or presently being operated on by processing unit **120**. By way of example, and not limitation, the FIGURE illustrates operating system **134**, application programs **135**, other program modules **136**, and program data **137**.

The computer **110** may also include other removable/non-removable, volatile/nonvolatile computer storage media. By way of example only, the FIGURE illustrates a hard disk drive **140** that reads from or writes to non-removable, nonvolatile magnetic media, a magnetic disk drive **151** that reads from or writes to a removable, nonvolatile magnetic disk **152**, and an optical disk drive **155** that reads from or writes to a removable, nonvolatile optical disk **156** such as a CD ROM or other optical media. Other removable/non-removable, volatile/nonvolatile computer storage media that can be used in the exemplary operating environment include, but are not limited to, magnetic tape cassettes, flash memory cards, digital versatile disks, digital video tape, solid state RAM, solid state ROM, and the like. The hard disk drive **141** is typically connected to the system bus **121** through a non-removable memory interface such as interface **140**, and magnetic disk drive **151** and optical disk drive **155** are typically connected to the system bus **121** by a removable memory interface, such as interface **150**.

The drives and their associated computer storage media discussed above and illustrated in the FIGURE, provide storage of computer readable instructions, data structures, program modules and other data for the computer **110**. In the FIGURE, for example, hard disk drive **141** is illustrated as storing operating system **144**, application programs **145**, other program modules **146**, and program data **147**. Note that these components can either be the same as or different from operating system **134**, application programs **135**, other program modules **136**, and program data **137**. Operating system **144**, application programs **145**, other program modules **146**, and program data **147** are given different numbers here to illustrate that, at a minimum, they are different copies. A user may enter commands and information into the computer **20** through input devices such as a keyboard **162** and pointing device **161**, commonly referred to as a mouse, trackball or touch pad. Other input devices (not shown) may include a microphone, joystick, game pad, satellite dish, scanner, or the like. These and other input devices are often connected to the processing unit **120** through a user input interface **160** that is coupled to the system bus, but may be connected by other interface and bus structures, such as a parallel port, game port or a universal serial bus (USB). A monitor **191** or other type of display device is also connected to the system bus **121** via an interface, such as a video interface **190**. In addition to the monitor, computers may also include other peripheral output devices such as speakers **197** and printer **196**, which may be connected through an output peripheral interface **190**.

The computer **110** may operate in a networked environment using logical connections to one or more remote computers, such as a remote computer **180**. The remote computer **180** may be a personal computer, a server, a router, a network PC, a peer device or other common network node, and typically includes many or all of the elements described above relative to the computer **110**, although only a memory storage device **181** has been illustrated in the FIGURE. The logical connections depicted in FIGURE include a local area network (LAN) **171** and a wide area network (WAN) **173**, but may also include other networks. Such networking environments are commonplace in offices, enterprise-wide computer networks, intranets and the Internet.

When used in a LAN networking environment, the computer **110** is connected to the LAN **171** through a network interface or adapter **170**. When used in a WAN networking environment, the computer **110** typically includes a modem **172** or other means for establishing communications over the WAN **173**, such as the Internet. The modem **172**, which may be internal or external, may be connected to the system bus **121** via the user input interface **160**, or other appropriate mechanism. In a networked environment, program modules depicted relative to the computer **110**, or portions thereof, may be stored in the remote memory storage device. By way of example, and not limitation, the FIGURE illustrates remote application programs **185** as residing on memory device **181**. It will be appreciated that the network connections shown are exemplary and other means of establishing a communications link between the computers may be used.

Although the forgoing text sets forth a detailed description of numerous different embodiments of the invention, it should be understood that the scope of the invention is defined by the words of the claims set forth at the end of this patent. The detailed description is to be construed as exemplary only and does not describe every possibly embodiment of the invention because describing every possible embodiment would be impractical, if not impossible. Numerous alternative embodiments could be implemented, using either current technology or technology developed after the filing date of this patent, which would still fall within the scope of the claims defining the invention.

While the risk evaluation system and method, and other elements, have been described as preferably being implemented in software, they may be implemented in hardware, firmware, etc., and may be implemented by any other processor. Thus, the elements described herein may be implemented in a standard multi-purpose CPU or on specifically designed hardware or firmware such as an application-specific integrated circuit (ASIC) or other hard-wired device as desired, including, but not limited to, the computer **110** of the FIGURE. When implemented in software, the software routine may be stored in any computer readable memory such as on a magnetic disk, a laser disk, or other storage medium, in a RAM or ROM of a computer or processor, in any database, etc. Likewise, this software may be delivered to a user or a diagnostic system via any known or desired delivery method including, for example, on a computer readable disk or other transportable computer storage mechanism or over a communication channel such as a telephone line, the interne, wireless communication, etc. (which are viewed as being the same as or interchangeable with providing such software via a transportable storage medium).

Thus, many modifications and variations may be made in the techniques and structures described and illustrated herein without departing from the spirit and scope of the present invention. Thus, it should be understood that the methods and apparatus described herein are illustrative only and are not limiting upon the scope of the invention.

Accordingly, the invention relates to computer-implemented applications using the polymorphic markers and haplotypes described herein, and genotype and/or disease-association data derived therefrom. Such applications can be useful for storing, manipulating or otherwise analyzing genotype data that is useful in the methods of the invention. One example pertains to storing genotype information derived from an individual on readable media, so as to be able to provide the genotype information to a third party (e.g., the individual, a guardian of the individual, a health care provider or genetic analysis service provider), or for deriving information from the genotype data, e.g., by comparing the genotype data to information about genetic risk factors contributing to

increased susceptibility to prostate and/or colorectal cancer, and reporting results based on such comparison.

In general terms, computer-readable media has capabilities of storing (i) identifier information for at least one polymorphic marker or a haplotype, as described herein; (ii) an indicator of the frequency of at least one allele of said at least one marker, or the frequency of a haplotype, in individuals with prostate cancer and/or colorectal cancer; and an indicator of the frequency of at least one allele of said at least one marker, or the frequency of a haplotype, in a reference population. The reference population can be a disease-free population of individuals. Alternatively, the reference population is a random sample from the general population, and is thus representative of the population at large. The frequency indicator may be a calculated frequency, a count of alleles and/or haplotype copies, or normalized or otherwise manipulated values of the actual frequencies that are suitable for the particular medium.

The markers and haplotypes described herein to be associated with increased susceptibility (e.g., increased risk) of prostate and colorectal cancer, are in certain embodiments useful for interpretation and/or analysis of genotype data. Thus in certain embodiments, an identification of an at-risk allele for prostate cancer and/or colorectal cancer, as shown herein, or an allele at a polymorphic marker in LD with any one of the markers shown herein to be associated with these cancers, is indicative of the individual from whom the genotype data originates is at increased risk of prostate cancer and/or colorectal cancer. In one such embodiment, genotype data is generated for at least one such polymorphic marker, or a marker in linkage disequilibrium therewith. The genotype data is subsequently made available to a third party, such as the individual from whom the data originates, his/her guardian or representative, a physician or health care worker, genetic counselor, or insurance agent, for example via a user interface accessible over the internet, together with an interpretation of the genotype data, e.g., in the form of a risk measure (such as an absolute risk (AR), risk ratio (RR) or odds ratio (OR)) for the disease. In another embodiment, at-risk markers identified in a genotype dataset derived from an individual are assessed and results from the assessment of the risk conferred by the presence of such at-risk variants in the dataset are made available to the third party, for example via a secure web interface, or by other communication means. The results of such risk assessment can be reported in numeric form (e.g., by risk values, such as absolute risk, relative risk, and/or an odds ratio, or by a percentage increase in risk compared with a reference), by graphical means, or by other means suitable to illustrate the risk to the individual from whom the genotype data is derived.

Nucleic Acids and Polypeptides

The nucleic acids and polypeptides described herein can be used in methods an kits of the present invention, as described in the above.

An "isolated" nucleic acid molecule, as used herein, is one that is separated from nucleic acids that normally flank the gene or nucleotide sequence (as in genomic sequences) and/or has been completely or partially purified from other transcribed sequences (e.g., as in an RNA library). For example, an isolated nucleic acid of the invention can be substantially isolated with respect to the complex cellular milieu in which it naturally occurs, or culture medium when produced by recombinant techniques, or chemical precursors or other chemicals when chemically synthesized. In some instances, the isolated material will form part of a composition (for example, a crude extract containing other substances), buffer system or reagent mix. In other circumstances, the material can be purified to essential homogeneity, for example as determined by polyacrylamide gel electrophoresis (PAGE) or column chromatography (e.g., HPLC). An isolated nucleic acid molecule of the invention can comprise at least about 50%, at least about 80% or at least about 90% (on a molar basis) of all macromolecular species present. With regard to genomic DNA, the term "isolated" also can refer to nucleic acid molecules that are separated from the chromosome with which the genomic DNA is naturally associated. For example, the isolated nucleic acid molecule can contain less than about 250 kb, 200 kb, 150 kb, 100 kb, 75 kb, 50 kb, 25 kb, 10 kb, 5 kb, 4 kb, 3 kb, 2 kb, 1 kb, 0.5 kb or 0.1 kb of the nucleotides that flank the nucleic acid molecule in the genomic DNA of the cell from which the nucleic acid molecule is derived.

The nucleic acid molecule can be fused to other coding or regulatory sequences and still be considered isolated. Thus, recombinant DNA contained in a vector is included in the definition of "isolated" as used herein. Also, isolated nucleic acid molecules include recombinant DNA molecules in heterologous host cells or heterologous organisms, as well as partially or substantially purified DNA molecules in solution. "Isolated" nucleic acid molecules also encompass in vivo and in vitro RNA transcripts of the DNA molecules of the present invention. An isolated nucleic acid molecule or nucleotide sequence can include a nucleic acid molecule or nucleotide sequence that is synthesized chemically or by recombinant means. Such isolated nucleotide sequences are useful, for example, in the manufacture of the encoded polypeptide, as probes for isolating homologous sequences (e.g., from other mammalian species), for gene mapping (e.g., by in situ hybridization with chromosomes), or for detecting expression of the gene in tissue (e.g., human tissue), such as by Northern blot analysis or other hybridization techniques.

The invention also pertains to nucleic acid molecules that hybridize under high stringency hybridization conditions, such as for selective hybridization, to a nucleotide sequence described herein (e.g., nucleic acid molecules that specifically hybridize to a nucleotide sequence containing a polymorphic site associated with a marker or haplotype described herein). Such nucleic acid molecules can be detected and/or isolated by allele- or sequence-specific hybridization (e.g., under high stringency conditions). Stringency conditions and methods for nucleic acid hybridizations are well known to the skilled person (see, e.g., *Current Protocols in Molecular Biology*, Ausubel, F. et al, John Wiley & Sons, (1998), and Kraus, M. and Aaronson, S., *Methods Enzymol.,* 200:546-556 (1991), the entire teachings of which are incorporated by reference herein.

The percent identity of two nucleotide or amino acid sequences can be determined by aligning the sequences for optimal comparison purposes (e.g., gaps can be introduced in the sequence of a first sequence). The nucleotides or amino acids at corresponding positions are then compared, and the percent identity between the two sequences is a function of the number of identical positions shared by the sequences (i.e., % identity=# of identical positions/total # of positions× 100). In certain embodiments, the length of a sequence aligned for comparison purposes is at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95%, of the length of the reference sequence. The actual comparison of the two sequences can be accomplished by well-known methods, for example, using a mathematical algorithm. A non-limiting example of such a mathematical algorithm is described in Karlin, S, and Altschul, S., *Proc. Natl. Acad. Sci. USA,* 90:5873-5877 (1993). Such an algorithm is incorporated into the NBLAST and XBLAST

programs (version 2.0), as described in Altschul, S. et al., *Nucleic Acids Res.,* 25:3389-3402 (1997). When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (e.g., NBLAST) can be used. See the website on the world wide web at ncbi.nlm.nih.gov. In one embodiment, parameters for sequence comparison can be set at score=100, wordlength=12, or can be varied (e.g., W=5 or W=20).

Other examples include the algorithm of Myers and Miller, CABIOS (1989), ADVANCE and ADAM as described in Torellis, A. and Robotti, C., *Comput. Appl. Biosci.* 10:3-5 (1994); and FASTA described in Pearson, W. and Lipman, D., *Proc. Natl. Acad. Sci. USA,* 85:2444-48 (1988). In another embodiment, the percent identity between two amino acid sequences can be accomplished using the GAP program in the GCG software package (Accelrys, Cambridge, UK).

The present invention also provides isolated nucleic acid molecules that contain a fragment or portion that hybridizes under highly stringent conditions to a nucleic acid that comprises, or consists of, the nucleotide sequence of LD Block C06 and/or LD Block C11, as defined herein, or a nucleotide sequence comprising, or consisting of, the complement of the nucleotide sequence of LD Block C06 and/or LD Block C11, wherein the nucleotide sequence comprises at least one polymorphic allele contained in the markers and haplotypes described herein. The nucleic acid fragments of the invention are at least about 15, at least about 18, 20, 23 or 25 nucleotides, and can be 30, 40, 50, 100, 200, 500, 1000, 10,000 or more nucleotides in length.

The nucleic acid fragments of the invention are used as probes or primers in assays such as those described herein. "Probes" or "primers" are oligonucleotides that hybridize in a base-specific manner to a complementary strand of a nucleic acid molecule. In addition to DNA and RNA, such probes and primers include polypeptide nucleic acids (PNA), as described in Nielsen, P. et al., *Science* 254:1497-1500 (1991). A probe or primer comprises a region of nucleotide sequence that hybridizes to at least about 15, typically about 20-25, and in certain embodiments about 40, 50 or 75, consecutive nucleotides of a nucleic acid molecule. In one embodiment, the probe or primer comprises at least one allele of at least one polymorphic marker or at least one haplotype described herein, or the complement thereof. In particular embodiments, a probe or primer can comprise 100 or fewer nucleotides; for example, in certain embodiments from 6 to 50 nucleotides, or, for example, from 12 to 30 nucleotides. In other embodiments, the probe or primer is at least 70% identical, at least 80% identical, at least 85% identical, at least 90% identical, or at least 95% identical, to the contiguous nucleotide sequence or to the complement of the contiguous nucleotide sequence. In another embodiment, the probe or primer is capable of selectively hybridizing to the contiguous nucleotide sequence or to the complement of the contiguous nucleotide sequence. Often, the probe or primer further comprises a label, e.g., a radioisotope, a fluorescent label, an enzyme label, an enzyme co-factor label, a magnetic label, a spin label, an epitope label.

The nucleic acid molecules of the invention, such as those described above, can be identified and isolated using standard molecular biology techniques well known to the skilled person. The amplified DNA can be labeled (e.g., radiolabeled) and used as a probe for screening a cDNA library derived from human cells. The cDNA can be derived from mRNA and contained in a suitable vector. Corresponding clones can be isolated, DNA can obtained following in vivo excision, and the cloned insert can be sequenced in either or both orientations by art-recognized methods to identify the correct reading frame encoding a polypeptide of the appropriate molecular weight. Using these or similar methods, the polypeptide and the DNA encoding the polypeptide can be isolated, sequenced and further characterized.

Antibodies

The invention also provides antibodies which bind to an epitope comprising either a variant amino acid sequence (e.g., comprising an amino acid substitution) encoded by a variant allele or the reference amino acid sequence encoded by the corresponding non-variant or wild-type allele. The term "antibody" as used herein refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain antigen-binding sites that specifically bind an antigen. A molecule that specifically binds to a polypeptide of the invention is a molecule that binds to that polypeptide or a fragment thereof, but does not substantially bind other molecules in a sample, e.g., a biological sample, which naturally contains the polypeptide. Examples of immunologically active portions of immunoglobulin molecules include F(ab) and $F(ab')_2$ fragments which can be generated by treating the antibody with an enzyme such as pepsin. The invention provides polyclonal and monoclonal antibodies that bind to a polypeptide of the invention. The term "monoclonal antibody" or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one species of an antigen binding site capable of immunoreacting with a particular epitope of a polypeptide of the invention. A monoclonal antibody composition thus typically displays a single binding affinity for a particular polypeptide of the invention with which it immunoreacts.

Polyclonal antibodies can be prepared as described above by immunizing a suitable subject with a desired immunogen, e.g., polypeptide of the invention or a fragment thereof. The antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized polypeptide. If desired, the antibody molecules directed against the polypeptide can be isolated from the mammal (e.g., from the blood) and further purified by well-known techniques, such as protein A chromatography to obtain the IgG fraction. At an appropriate time after immunization, e.g., when the antibody titers are highest, antibody-producing cells can be obtained from the subject and used to prepare monoclonal antibodies by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein, *Nature* 256:495-497 (1975), the human B cell hybridoma technique (Kozbor et al., *Immunol. Today* 4: 72 (1983)), the EBV-hybridoma technique (Cole et al., *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, 1985, Inc., pp. 77-96) or trioma techniques. The technology for producing hybridomas is well known (see generally *Current Protocols in Immunology* (1994) Coligan et al., (eds.) John Wiley & Sons, Inc., New York, N.Y.). Briefly, an immortal cell line (typically a myeloma) is fused to lymphocytes (typically splenocytes) from a mammal immunized with an immunogen as described above, and the culture supernatants of the resulting hybridoma cells are screened to identify a hybridoma producing a monoclonal antibody that binds a polypeptide of the invention.

Any of the many well known protocols used for fusing lymphocytes and immortalized cell lines can be applied for the purpose of generating a monoclonal antibody to a polypeptide of the invention (see, e.g., *Current Protocols in Immunology*, supra; Galfre et al., *Nature* 266:55052 (1977); R. H. Kenneth, in *Monoclonal Antibodies: A New Dimension In Biological Analyses*, Plenum Publishing Corp., New York,

N.Y. (1980); and Lerner, *Yale J. Biol. Med.* 54:387-402 (1981)). Moreover, the ordinarily skilled worker will appreciate that there are many variations of such methods that also would be useful.

Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal antibody to a polypeptide of the invention can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (e.g., an antibody phage display library) with the polypeptide to thereby isolate immunoglobulin library members that bind the polypeptide. Kits for generating and screening phage display libraries are commercially available (e.g., the Pharmacia *Recombinant Phage Antibody System*, Catalog No. 27-9400-01; and the Stratagene SurfZAP™ Phage Display Kit, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, U.S. Pat. No. 5,223,409; PCT Publication No. WO 92/18619; PCT Publication No. WO 91/17271; PCT Publication No. WO 92/20791; PCT Publication No. WO 92/15679; PCT Publication No. WO 93/01288; PCT Publication No. WO 92/01047; PCT Publication No. WO 92/09690; PCT Publication No. WO 90/02809; Fuchs et al., *Bio/Technology* 9: 1370-1372 (1991); Hay et al., *Hum. Antibod. Hybridomas* 3:81-85 (1992); Huse et al., *Science* 246: 1275-1281 (1989); and Griffiths et al., *EMBO J.* 12:725-734 (1993).

Additionally, recombinant antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, which can be made using standard recombinant DNA techniques, are within the scope of the invention. Such chimeric and humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art.

In general, antibodies of the invention (e.g., a monoclonal antibody) can be used to isolate a polypeptide of the invention by standard techniques, such as affinity chromatography or immunoprecipitation. A polypeptide-specific antibody can facilitate the purification of natural polypeptide from cells and of recombinantly produced polypeptide expressed in host cells. Moreover, an antibody specific for a polypeptide of the invention can be used to detect the polypeptide (e.g., in a cellular lysate, cell supernatant, or tissue sample) in order to evaluate the abundance and pattern of expression of the polypeptide. Antibodies can be used diagnostically to monitor protein levels in tissue as part of a clinical testing procedure, e.g., to, for example, determine the efficacy of a given treatment regimen. The antibody can be coupled to a detectable substance to facilitate its detection. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ^{125}I, ^{131}I, ^{35}S or ^{3}H.

Antibodies may also be useful in pharmacogenomic analysis. In such embodiments, antibodies against variant proteins encoded by nucleic acids according to the invention, such as variant proteins that are encoded by nucleic acids that contain at least one polymorphic marker of the invention, can be used to identify individuals that require modified treatment modalities.

Antibodies can furthermore be useful for assessing expression of variant proteins in disease states, such as in active stages of a cancer, such as prostate cancer and/or colorectal cancer, or in an individual with a predisposition to a cancer related to the function of the protein, in particular prostate cancer and colorectal cancer. Antibodies specific for a variant protein of the present invention that is encoded by a nucleic acid that comprises at least one polymorphic marker or haplotype as described herein can be used to screen for the presence of the variant protein, for example to screen for a predisposition to prostate cancer and/or colorectal cancer, as indicated by the presence of the variant protein.

Antibodies can be used in other methods. Thus, antibodies are useful as diagnostic tools for evaluating proteins, such as variant proteins of the invention, in conjunction with analysis by electrophoretic mobility, isoelectric point, tryptic or other protease digest, or for use in other physical assays known to those skilled in the art. Antibodies may also be used in tissue typing. In one such embodiment, a specific variant protein has been correlated with expression in a specific tissue type, and antibodies specific for the variant protein can then be used to identify the specific tissue type.

Subcellular localization of proteins, including variant proteins, can also be determined using antibodies, and can be applied to assess aberrant subcellular localization of the protein in cells in various tissues. Such use can be applied in genetic testing, but also in monitoring a particular treatment modality. In the case where treatment is aimed at correcting the expression level or presence of the variant protein or aberrant tissue distribution or developmental expression of the variant protein, antibodies specific for the variant protein or fragments thereof can be used to monitor therapeutic efficacy.

Antibodies are further useful for inhibiting variant protein function, for example by blocking the binding of a variant protein to a binding molecule or partner. Such uses can also be applied in a therapeutic context in which treatment involves inhibiting a variant protein's function. An antibody can be for example be used to block or competitively inhibit binding, thereby modulating (i.e., agonizing or antagonizing) the activity of the protein. Antibodies can be prepared against specific protein fragments containing sites required for specific function or against an intact protein that is associated with a cell or cell membrane. For administration in vivo, an antibody may be linked with an additional therapeutic payload, such as radionuclide, an enzyme, an immunogenic epitope, or a cytotoxic agent, including bacterial toxins (diphtheria or plant toxins, such as ricin). The in vivo half-life of an antibody or a fragment thereof may be increased by pegylation through conjugation to polyethylene glycol.

The present invention further relates to kits for using antibodies in the methods described herein. This includes, but is not limited to, kits for detecting the presence of a variant protein in a test sample. One preferred embodiment comprises antibodies such as a labelled or labelable antibody and a compound or agent for detecting variant proteins in a biological sample, means for determining the amount or the presence and/or absence of variant protein in the sample, and means for comparing the amount of variant protein in the sample with a standard, as well as instructions for use of the kit.

The present invention will now be exemplified by the following non-limiting example.

EXEMPLIFICATION

Example 1

Identification of Markers and LD Block Regions Associated with Prostate Cancer

Patients Involved in the Genetics Study

A population based list of all prostate and colorectal cancer patients that were diagnosed in Iceland from 1955 to 2005 form the basis for this study. Patients have been invited to join the study since 2001 on an ongoing basis. As of June 2007, blood samples from 1,850 prostate cancer and 1,169 colorectal cancer patients have been recruited. Genomic DNA from those samples, as well as samples from over 27,000 control individuals was extracted and genotyped.

Genotyping

A genome-wide scan of 1,645 Icelandic individuals diagnosed with Prostate Cancer, 1,010 colorectal cancer patients and 27,049 population controls was performed using Infinium HumanHap300 SNP chips from Illumina for assaying approximately 317,000 single nucleotide polymorphisms (SNPs) on a single chip (Illumina, San Diego, Calif., USA). SNP genotyping for replication in other case-control cohorts was carried using the Centaurus platform (Nanogen).

Statistical Methods for Association and Haplotype Analysis

For single marker association to the disease, Fisher exact test was used to calculate a two-sided P-value for each individual allele. When presenting the results, we used allelic frequencies rather than carrier frequencies for SNPs and haplotypes. The program NEMO (NEsted Models; Gretarsdottir, et al., *Nat. Genet.* 2003 October; 35(2):131-8) was used both to study marker-marker association and to calculate linkage disequilibrium (LD) between markers. With NEMO, haplotype frequencies are estimated by maximum likelihood and the differences between patients and controls are tested using a generalized likelihood ratio test. The maximum likelihood estimates, likelihood ratios and P-values are computed with the aid of the EM-algorithm directly for the observed data, and hence the loss of information due to the uncertainty with phase and missing genotypes is automatically captured by the likelihood ratios, and under most situations, large sample theory can be used to reliably determine statistical significance. The relative risk (RR) of an allele or a haplotype, i.e., the risk of an allele compared to all other alleles of the same marker, is calculated assuming the multiplicative model (Terwilliger, J. D. & Ott, J. A haplotype-based 'haplotype relative risk' approach to detecting allelic associations. *Hum. Hered.* 42, 337-46 (1992) and Falk, C. T. & Rubinstein, P. Haplotype relative risks: an easy reliable way to construct a proper control sample for risk calculations. *Ann. Hum. Genet.* 51 (Pt 3), 227-33 (1987)), together with the population attributable risk (PAR). When controls are considered unaffected (i.e., disease-free), the relative risk is replaced by an estimate for the odds ratio (OR) of the particular marker allele or haplotype.

As a measure of LD, we use two standard definitions of LD, D' and R^2 (Lewontin, R., *Genetics,* 49:49-67 (1964) and Hill, W. G. and A. Robertson, *Theor. Appl. Genet.,* 22:226-231 (1968)) as they provide complementary information on the amount of LD. For the purpose of estimating D' and R^2, the frequencies of all two-marker allele combinations are estimated using maximum likelihood methods and the deviation from linkage disequilibrium is evaluated using a likelihood ratio test. The standard definitions of D' and R^2 are extended to include microsatellites by averaging over the values for all possible allele combinations of the two markers weighted by the marginal allele probabilities.

Results

Through analysis of over 300,000 markers across the genome, we identified two regions that are associated with prostate and colorectal cancer. In Table 1, we show results of association of markers rs10896450 and rs7947353 on Chr 11q13.3 to prostate cancer. The two markers are fully correlated (D'=1 and r^2=1; see footnote of Table 1) and do therefore essentially represent the same association signal The G allele of SNP marker rs10896450 confers increased risk of prostate cancer, with an odds ratio (OR) of 1.17 in the Icelandic samples ($P=6.6\times10^{-5}$).

To validate the initial discovery, we attempted to genotype the rs10896450 SNP marker in prostate cancer cohorts from the Netherlands, Spain and US (Chicago, Ill.). However, the design of the Centaurus assay failed for this marker and we therefore selected a fully correlated SNP rs7947353 (D'=1 and r^2=1; see footnote of Table 1) for further genotyping and analysis in the replication samples. The results for allele A of SNP marker rs7947353 from the replication cohorts are shown in Table 1, and are comparable to the results for the Icelandic discovery cohort. The observed risk in the Spanish cohort is somewhat lower than in Iceland, while the US cohort has a higher risk. Overall, the association is significant with a p-value of 1.43×10^{6}.

A second association signal was detected on Chromosome 6 for prostate cancer (Table 2a). The signal was replicated in Dutch and Spanish cohort, both which gave increased risk conferred by the G allele of the rs10943605 SNP marker, although only the replication in the Dutch cohort is statistically significant. The G allele of the rs10943605 SNP marker was also found to be associated with increased risk of developing colorectal cancer, with an OR of 1.14 in the Icelandic colorectal cancer samples ($P=4.8\times10^{-3}$) (Table 2b).

TABLE 1

Association results for 11q13.3 and prostate cancer in Iceland discovery cohort, and replication cohorts from The Netherlands, Spain, and the US

Study population (N cases/N controls)	Frequency			
Variant (allele)	Cases	Controls	OR	P value
Iceland (1,645/21,474)				
rs10896450 (G)[a]	0.505	0.466	1.17	6.6×10^{-5}
rs7947353 (A)[a]	0.505	0.466	1.17	6.6×10^{-5}
The Netherlands (998/2,014)				
rs7947353 (A)	0.528	0.500	1.12	0.042
Spain (455/1,066)				
rs7947353 (A)	0.579	0.564	1.06	0.450
Chicago, Illinois (661/292)				
rs7947353 (A)	0.545	0.493	1.23	0.035
All above combined (3,759/24,846)				
rs7947353 (A)	—	0.506	1.15	1.43×10^{-6}

TABLE 1-continued

[a]Correlation between the two markers see below (results are based on analysis of 2,340 Icelanders:

M1	M2	D'	r^2
rs10896450	rs7947353	1	1

TABLE 2a

Association results for 6q14.1 and prostate cancer in Icelandic discovery cohorts, and replication cohorts from The Netherlands and Spain.

Study population (N cases/N controls)	Frequency			
Variant (allele)	Cases	Controls	OR	P value
Iceland PrCa (1,645/21,472)				
rs10943605 (G)	0.597	0.557	1.18	2.72×10^{-5}
The Netherlands PrCa (910/2,006)				
rs10943605 (G)	0.530	0.490	1.17	6.04×10^{-3}
Spain PrCa (436/1,417)				
rs10943605 (G)	0.567	0.553	1.06	0.480

TABLE 2a-continued

Association results for 6q14.1 and prostate cancer in Icelandic discovery cohorts, and replication cohorts from The Netherlands and Spain.

Study population (N cases/N controls)	Frequency			
Variant (allele)	Cases	Controls	OR	P value
All above combined (2,991/24,895)				
rs10943605 (G)	—	0.533	1.16	9.35×10^{-7}

TABLE 2b

Association results for 6q14.1 and colorectal cancer in Iceland

Study population (N cases/N controls) Variant (allele)	Frequency			
Iceland ColCa (1,010/27,033)	Cases	Controls	OR	P value
rs10943605 (G)	0.591	0.558	1.14	4.8×10^{-3}

TABLE 3

SNP markers that are in linkage disequilibrium with marker rs10943605 on Chromosome 6. Linkage disequilibrium was calculated based on HapMap CEU population data (http://www.hapmap.org). Location of correlated markers is given with respect to NCBI Build 36 of the Human genome assembly.

Marker 1	Marker 2	D'	r^2	p-value	Marker 1 location	Seq ID No:
rs611737	rs10943605	0.631963	0.293866	3.91E−09	79300773	1
rs666982	rs10943605	0.605842	0.284949	6.11E−09	79316431	2
rs685245	rs10943605	0.606322	0.29663	1.77E−08	79327502	3
rs547472	rs10943605	0.608391	0.291941	4.51E−09	79341083	4
rs654628	rs10943605	0.603324	0.288712	6.47E−09	79343805	5
rs605697	rs10943605	0.622444	0.296062	6.91E−09	79345910	6
rs605264	rs10943605	0.605842	0.284949	6.11E−09	79346003	7
rs603964	rs10943605	0.609097	0.293439	6.80E−09	79346271	8
rs612489	rs10943605	0.604036	0.290201	9.72E−09	79346309	9
rs484582	rs10943605	0.610497	0.30416	4.78E−09	79346824	10
rs597283	rs10943605	0.572594	0.27296	3.74E−08	79347449	11
rs596810	rs10943605	0.590052	0.272681	2.36E−08	79347562	12
rs596337	rs10943605	0.600542	0.282979	1.11E−08	79347676	13
rs655566	rs10943605	0.597614	0.277093	1.90E−08	79348564	14
rs689389	rs10943605	0.608391	0.291941	4.51E−09	79348661	15
rs846452	rs10943605	0.60564	0.286192	7.77E−09	79348887	16
rs674105	rs10943605	0.605842	0.284949	6.11E−09	79349688	17
rs236867	rs10943605	0.605842	0.284949	6.11E−09	79355383	18
rs236872	rs10943605	0.593491	0.304327	7.89E−09	79358008	19
rs236873	rs10943605	0.592785	0.282009	1.33E−08	79358580	20
rs236877	rs10943605	0.608391	0.291941	4.51E−09	79362203	21
rs70478	rs10943605	0.564166	0.209862	3.01E−06	79364899	22
rs70480	rs10943605	0.568404	0.216181	1.39E−06	79365324	23
rs236882	rs10943605	0.695923	0.256498	5.08E−08	79372832	24
rs236884	rs10943605	0.700831	0.26597	3.12E−08	79376244	25
rs236888	rs10943605	0.741063	0.286153	1.20E−08	79378960	26
rs236861	rs10943605	0.689267	0.264436	2.73E−07	79390866	27
rs236862	rs10943605	0.65937	0.248439	1.40E−07	79391691	28
rs236855	rs10943605	0.74615	0.29984	5.25E−09	79398610	29
rs12210702	rs10943605	0.886957	0.355449	2.28E−11	79426052	30
rs9359338	rs10943605	0.897621	0.450682	1.86E−13	79453470	31
rs9352611	rs10943605	0.89472	0.436416	7.36E−13	79453687	32
rs10943567	rs10943605	0.901397	0.4471	6.06E−14	79459170	33
rs10943568	rs10943605	0.898063	0.444367	5.16E−13	79460926	34
rs9343786	rs10943605	0.901397	0.4471	6.06E−14	79471447	35
rs4706718	rs10943605	0.901397	0.4471	6.06E−14	79473602	36
rs9341739	rs10943605	0.899434	0.433323	2.58E−13	79475795	37
rs9352613	rs10943605	0.901397	0.4471	6.06E−14	79481152	38
rs13198615	rs10943605	0.620748	0.264225	2.31E−08	79487271	39

TABLE 3-continued

SNP markers that are in linkage disequilibrium with marker rs10943605 on Chromosome 6. Linkage disequilibrium was calculated based on HapMap CEU population data (http://www.hapmap.org). Location of correlated markers is given with respect to NCBI Build 36 of the Human genome assembly.

Marker 1	Marker 2	D'	r^2	p-value	Marker 1 location	Seq ID No:
rs1180823	rs10943605	0.786316	0.274692	3.17E−09	79489645	40
rs1180828	rs10943605	0.620748	0.264225	2.31E−08	79492141	41
rs9343798	rs10943605	0.620748	0.264225	2.31E−08	79512001	42
rs7382016	rs10943605	0.620748	0.264225	2.31E−08	79512500	43
rs7759829	rs10943605	1	0.257426	5.01E−10	79513725	44
rs7759687	rs10943605	0.910286	0.229805	3.16E−07	79513734	45
rs9361426	rs10943605	0.620748	0.264225	2.31E−08	79514269	46
rs1158575	rs10943605	0.620748	0.264225	2.31E−08	79515925	47
rs9359344	rs10943605	0.620748	0.264225	2.31E−08	79517752	48
rs4141594	rs10943605	0.502039	0.207557	9.50E−07	79517914	49
rs9343820	rs10943605	1	0.87395	2.70E−31	79537177	50
rs1876389	rs10943605	0.824869	0.421093	3.32E−13	79538651	51
rs1021987	rs10943605	1	0.21875	2.66E−09	79539884	52
rs1507152	rs10943605	0.83431	0.329234	2.01E−10	79540193	53
rs1507153	rs10943605	1	0.509466	2.18E−18	79541105	54
rs9343824	rs10943605	1	0.537205	1.54E−18	79554288	55
rs1507149	rs10943605	0.960507	0.683059	4.95E−22	79556805	56
rs9343827	rs10943605	1	0.967033	1.10E−35	79557755	57
rs6926463	rs10943605	0.942137	0.382849	1.82E−12	79559890	58
rs9361448	rs10943605	1	0.300546	1.55E−11	79579645	59
rs12195716	rs10943605	1	0.967033	1.10E−35	79592131	60
rs6902294	rs10943605	1	0.21875	2.66E−09	79593001	61
rs1567168	rs10943605	1	0.967033	1.10E−35	79593174	62
rs2135767	rs10943605	0.943831	0.389733	6.65E−13	79593386	63
rs9352662	rs10943605	0.939889	0.390142	2.32E−11	79598210	64
rs1027813	rs10943605	1	1	1.22E−37	79608837	65
rs1567167	rs10943605	1	1	1.14E−36	79610546	66
rs12196485	rs10943605	1	0.550265	1.01E−19	79613590	67
rs9352663	rs10943605	1	0.550265	1.01E−19	79614883	68
rs971994	rs10943605	1	1	9.93E−37	79616321	69
rs4421161	rs10943605	1	1	6.05E−38	79620938	70
rs12176511	rs10943605	1	0.715909	1.15E−25	79622440	71
rs9352664	rs10943605	1	1	6.05E−38	79622881	72
rs9352666	rs10943605	1	1	2.00E−36	79628903	73
rs9352667	rs10943605	1	1	6.05E−38	79629015	74
rs9352668	rs10943605	1	0.715909	2.11E−25	79629397	75
rs9448584	rs10943605	1	1	6.05E−38	79629518	76
rs9361459	rs10943605	1	0.715909	7.04E−25	79629641	77
rs9341753	rs10943605	1	0.361702	6.05E−14	79634515	78
rs9352669	rs10943605	1	1	2.00E−36	79640860	79
rs9341754	rs10943605	1	0.966443	8.10E−35	79641692	80
rs9343844	rs10943605	1	1	1.30E−37	79643182	81
rs9350792	rs10943605	1	0.550265	1.01E−19	79643892	82
rs9361460	rs10943605	1	1	6.05E−38	79646186	83
rs9359354	rs10943605	1	1	8.67E−36	79647104	84
rs2174743	rs10943605	1	1	1.30E−37	79648524	85
rs6908105	rs10943605	1	0.516024	7.87E−19	79651816	86
rs12192086	rs10943605	1	0.360294	5.04E−14	79657229	87
rs2174742	rs10943605	1	1	1.22E−37	79666820	88
rs9352675	rs10943605	1	1	2.30E−37	79669519	89
rs1354832	rs10943605	1	0.966849	1.92E−35	79670482	90
rs4706079	rs10943605	1	1	2.00E−36	79671927	91
rs7756858	rs10943605	1	1	2.45E−37	79676687	92
rs9448594	rs10943605	1	0.355054	2.69E−12	79679933	93
rs12196457	rs10943605	1	0.550265	1.01E−19	79684462	94
rs9343853	rs10943605	1	0.375	1.67E−14	79699300	95
rs7740307	rs10943605	1	0.525	2.34E−19	79710873	96
rs10943605	rs10943605	1	1	—	79712196	97
rs2275291	rs10943605	1	0.351955	9.65E−13	79713281	98
rs2275290	rs10943605	1	0.525	3.77E−19	79713289	99
rs1984195	rs10943605	1	1	1.30E−37	79714110	100
rs2174739	rs10943605	1	1	1.14E−37	79715889	101
rs9448600	rs10943605	1	0.525	2.34E−19	79719788	102
rs3805746	rs10943605	1	0.525	3.77E−19	79729157	103
rs3805747	rs10943605	1	1	1.22E−37	79729241	104
rs10943608	rs10943605	1	0.565217	6.62E−20	79731648	105
rs9350797	rs10943605	1	0.360294	5.04E−14	79732420	106
rs11964204	rs10943605	1	0.525	2.34E−19	79732781	107
rs9343856	rs10943605	1	1	1.30E−37	79734930	108
rs1538235	rs10943605	1	1	7.59E−37	79746169	109
rs1572584	rs10943605	1	1	6.05E−38	79747009	110
rs1572585	rs10943605	1	1	3.77E−36	79747295	111

TABLE 3-continued

SNP markers that are in linkage disequilibrium with marker rs10943605 on Chromosome 6. Linkage disequilibrium was calculated based on HapMap CEU population data (http://www.hapmap.org). Location of correlated markers is given with respect to NCBI Build 36 of the Human genome assembly.

Marker 1	Marker 2	D'	r^2	p-value	Marker 1 location	Seq ID No:
rs1890229	rs10943605	1	1	6.05E−38	79751748	112
rs3818839	rs10943605	1	0.380941	1.44E−14	79757044	113
rs9359360	rs10943605	1	0.575195	7.14E−19	79759515	114
rs9359361	rs10943605	1	0.367498	1.07E−13	79762302	115
rs9361477	rs10943605	1	0.558824	9.59E−20	79767525	116
rs9448607	rs10943605	1	0.757211	5.03E−26	79772339	117
rs9352683	rs10943605	1	1	4.94E−36	79775514	118
rs9443638	rs10943605	1	1	2.00E−36	79777586	119
rs4706747	rs10943605	1	1	1.30E−37	79779358	120
rs9361480	rs10943605	1	1	2.89E−34	79781148	121
rs1338023	rs10943605	1	0.365871	4.42E−14	79785047	122
rs2050660	rs10943605	1	1	6.05E−38	79791445	123
rs9448610	rs10943605	1	0.733202	5.86E−26	79796341	124
rs1538233	rs10943605	1	1	6.05E−38	79800454	125
rs9343861	rs10943605	1	0.509466	2.18E−18	79801587	126
rs10943613	rs10943605	1	0.740385	5.66E−26	79801826	127
rs11758432	rs10943605	1	0.375	1.67E−14	79806313	128
rs9361482	rs10943605	1	0.733202	2.00E−25	79807104	129
rs9343863	rs10943605	1	1	6.05E−38	79809511	130
rs2050663	rs10943605	1	1	2.30E−37	79810113	131
rs9448616	rs10943605	1	0.360294	5.04E−14	79813653	132
rs9352686	rs10943605	1	1	2.45E−37	79814942	133
rs2152951	rs10943605	1	1	6.05E−38	79818891	134
rs9343865	rs10943605	1	0.368421	4.53E−14	79821914	135
rs9343867	rs10943605	1	0.364105	5.50E−14	79829072	136
rs1547731	rs10943605	1	1	1.14E−37	79832823	137
rs9352688	rs10943605	1	0.360294	5.04E−14	79832882	138
rs10455120	rs10943605	1	0.444999	1.18E−15	79836486	139
rs9343869	rs10943605	1	0.360294	7.16E−14	79841140	140
rs9352691	rs10943605	1	0.550265	1.01E−19	79842326	141
rs7753531	rs10943605	1	0.709974	7.37E−25	79846715	142
rs7776138	rs10943605	1	0.375	1.67E−14	79851212	143
rs9359364	rs10943605	0.947194	0.482034	1.37E−13	79852711	144
rs9352693	rs10943605	1	0.352274	3.20E−13	79854791	145
rs7767100	rs10943605	0.964821	0.930648	1.26E−29	79867252	146
rs9443644	rs10943605	0.937107	0.333308	3.02E−11	79867363	147
rs12197385	rs10943605	1	0.266602	4.88E−10	79872695	148
rs9361489	rs10943605	0.965965	0.933016	1.07E−31	79873504	149
rs949846	rs10943605	0.950814	0.497465	6.74E−16	79874315	150
rs6916081	rs10943605	0.941241	0.345568	4.80E−12	79874571	151
rs1415310	rs10943605	0.856953	0.419639	3.80E−13	79879033	152
rs9443645	rs10943605	0.931848	0.839777	1.03E−27	79879643	153
rs10943616	rs10943605	0.853077	0.40045	1.48E−12	79880260	154
rs6940949	rs10943605	0.876626	0.288616	1.29E−09	79880754	155
rs7768535	rs10943605	0.930436	0.292034	1.28E−09	79892231	156
rs3920791	rs10943605	0.869223	0.261765	6.14E−09	79893453	157
rs1361043	rs10943605	0.873498	0.269641	3.81E−09	79893786	158
rs9343876	rs10943605	0.806769	0.225158	1.01E−07	79901219	159
rs9352701	rs10943605	0.876903	0.28836	1.27E−09	79916596	160
rs9361497	rs10943605	0.876903	0.28836	1.27E−09	79916649	161
rs9294130	rs10943605	0.746969	0.282652	8.22E−09	79917888	162

TABLE 4

SNP markers that are in linkage disequilibrium with marker rs10896450 on Chromosome 11. Linkage disequilibrium was calculated based on HapMap CEU population data (http://www.hapmap.org). Location of correlated markers is given with respect to NCBI Build 36 of the Human genome assembly.

Marker 1	Marker 2	D'	r^2	p-value	Marker 1 location	Seq ID No:	Pos in Seq ID: 201
rs7128814	rs10896450	0.754033	0.328273	7.44E−09	68709630	163	300
rs10896444	rs10896450	0.950801	0.522291	5.93E−15	68723823	164	14493
rs10896445	rs10896450	0.951635	0.522873	3.85E−15	68724217	165	14887
rs4255548	rs10896450	1	0.620339	2.97E−22	68730546	166	21216
rs7117034	rs10896450	1	0.257642	2.43E−10	68731718	167	22388
rs4495900	rs10896450	1	0.606213	5.17E−21	68732695	168	23365
rs11228563	rs10896450	1	0.373812	1.43E−13	68733572	169	24242

TABLE 4-continued

SNP markers that are in linkage disequilibrium with marker rs10896450 on Chromosome 11. Linkage disequilibrium was calculated based on HapMap CEU population data (http://www.hapmap.org). Location of correlated markers is given with respect to NCBI Build 36 of the Human genome assembly.

Marker 1	Marker 2	D'	r^2	p-value	Marker 1 location	Seq ID No:	Pos in Seq ID: 201
rs12281017	rs10896450	1	0.295093	8.65E−11	68734077	170	24747
rs11228565	rs10896450	1	0.249586	7.96E−10	68735156	171	25826
rs4620729	rs10896450	1	1	4.70E−38	68736911	172	27581
rs11821008	rs10896450	1	0.329609	1.51E−12	68737211	173	27881
rs11825796	rs10896450	1	0.311982	7.96E−12	68737364	174	28034
rs4451736	rs10896450	1	0.964531	2.83E−34	68739279	175	29949
rs12278923	rs10896450	1	0.959809	3.04E−31	68740137	176	30807
rs7929962	rs10896450	1	1	4.70E−38	68742159	177	32829
rs7109672	rs10896450	1	0.967195	8.12E−36	68747686	178	38356
rs10896448	rs10896450	1	1	4.70E−38	68748325	179	38995
rs12795301	rs10896450	1	0.241803	5.99E−10	68748861	180	39531
rs7122190	rs10896450	1	0.967195	8.12E−36	68750364	181	41034
rs6591374	rs10896450	1	1	1.90E−37	68750408	182	41078
rs7931342	rs10896450	1	0.967195	1.58E−35	68751073	183	41743
rs10896449	rs10896450	1	1	4.70E−38	68751243	184	41913
rs7130881	rs10896450	1	0.241803	5.99E−10	68752534	185	43204
rs12362678	rs10896450	1	0.967195	8.12E−36	68752746	186	43416
rs9787877	rs10896450	1	1	4.70E−38	68753085	187	43755
rs11603288	rs10896450	1	0.242151	1.13E−09	68753358	188	44028
rs4644650	rs10896450	1	0.967195	8.12E−36	68754694	189	45364
rs7950547	rs10896450	0.953052	0.582711	4.00E−15	68755364	190	46034
rs11228580	rs10896450	1	0.229339	1.58E−09	68758918	191	49588
rs7939250	rs10896450	1	1	1.87E−37	68759526	192	50196
rs7106762	rs10896450	1	1	4.70E−38	68760282	193	50952
rs12417087	rs10896450	1	0.221577	3.17E−09	68760555	194	51225
rs11228581	rs10896450	1	0.337143	7.39E−13	68760586	195	51256
rs7947353	rs10896450	1	1	1.19E−35	68761559	196	52229
rs10896450	rs10896450	1	1	—	68764690	197	55360
rs11228583	rs10896450	1	0.965547	6.06E−35	68765690	198	56360
rs12799883	rs10896450	1	1	1.90E−37	68767227	199	57897
rs3884627	rs10896450	1	0.425723	6.96E−16	68782375	200	73045

TABLE 5

Polymorphic markers within the C11 region, between position 68,709,630 and 68,782,375 in NCBI Build 36. Shown is marker ID (rs-names), position in Build 36, strand and polymorphism type, where (—/N), N being any one nucleotide, or a plurality of nucleotides, corresponding to an insertion/deletion polymorphism (i.e. either the nucleotide(s) is present or not).

Marker ID	Position Build 36	Strand	Polymorphism
rs7128814	68709630	+	A/G
rs34033330	68709734	+	—/T
rs4993568	68709920	+	G/T
rs4993567	68709926	+	C/G
rs11228548	68710333	+	C/T
rs11228549	68710384	+	C/T
rs10896441	68710484	+	A/G
rs10792027	68710514	+	C/G
rs10792028	68710515	+	C/T
rs11228550	68710833	+	C/T
rs12294054	68711092	+	A/G
rs11228551	68711570	+	A/T
rs11228552	68711592	+	C/T
rs10219207	68713596	+	A/G
rs12809032	68713686	+	C/T
rs11606280	68713966	+	A/G
rs35691765	68715000	+	—/G
rs4495899	68715236	+	G/T
rs12800787	68715895	+	C/T
rs4930664	68715976	+	A/G
rs4930665	68715984	+	A/T
rs4072598	68716265	–	G/T
rs1128553	68716760	+	G/T
rs10896442	68716789	+	A/G
rs12223972	68716967	+	A/G
rs12796709	68719501	+	A/C
rs34461339	68719872	+	—/G
rs12803641	68720487	+	C/T
rs12808650	68720536	+	C/G
rs12808185	68720581	+	A/C
rs12808690	68720599	+	C/G
rs12808846	68720638	+	C/G
rs12808599	68720804	+	A/T
rs12808603	68720810	+	A/T
rs12785256	68720824	+	A/G
rs11228554	68720854	+	C/T
rs11602052	68721150	+	C/G
rs11433399	68721158	+	—/G
rs10896443	68722211	+	G/T
rs11228555	68722341	+	C/T
rs10792029	68723458	+	A/G
rs4930666	68723812	+	C/T
rs10896444	68723823	+	A/C
rs34531633	68724028	+	G/T
rs11228556	68724029	+	G/T
rs10896445	68724217	+	C/T
rs11228557	68724542	+	A/G
rs10792030	68725391	+	A/G
rs12417971	68726384	+	C/T
rs11383798	68726876	+	—/G

TABLE 5-continued

Polymorphic markers within the C11 region, between position 68,709,630 and 68,782,375 in NCBI Build 36. Shown is marker ID (rs-names), position in Build 36, strand and polymorphism type, where (—/N), N being any one nucleotide, or a plurality of nucleotides, corresponding to an insertion/deletion polymorphism (i.e. either the nucleotide(s) is present or not).

Marker ID	Position Build 36	Strand	Polymorphism
rs7126286	68726993	+	C/T
rs34210900	68727006	+	—/G
rs3934653	68727096	–	A/C
rs12049842	68727624	+	G/T
rs9783326	68727749	+	C/T
rs7927331	68729100	+	A/G
rs7930375	68729233	+	C/G
rs7945442	68729323	+	C/T
rs9783278	68729551	+	A/C
rs9783279	68729568	+	A/C
rs9783280	68729612	+	A/G
rs11824548	68729893	+	A/G
rs7934295	68730254	+	C/T
rs4255548	68730546	+	A/G
rs7483742	68730628	+	G/T
rs7949811	68730632	+	G/T
rs12792553	68730645	+	A/C
rs12792562	68730662	+	A/C
rs12793009	68730931	+	C/T
rs12793759	68731131	+	A/G
rs9943593	68731168	+	A/G
rs11228558	68731439	+	C/T
rs10896446	68731695	+	C/T
rs7117034	68731718	+	C/T
rs11228559	68731861	+	C/T
rs11228560	68731965	+	C/T
rs7926098	68732100	+	C/T
rs12287117	68732101	+	C/G
rs7942465	68732362	+	C/T
rs11228561	68732444	+	C/G
rs7929389	68732558	+	A/T
rs4495900	68732695	+	C/T
rs11228562	68732747	+	G/T
rs11228563	68733572	+	A/G
rs10792031	68733592	+	A/G
rs12418968	68733711	+	C/T
rs12281017	68734077	+	A/G
rs4930667	68734625	+	C/T
rs12422130	68734751	+	A/G
rs11228564	68735154	+	C/T
rs11228565	68735156	+	A/G
rs4357697	68735224	+	G/T
rs7926037	68735253	+	C/G
rs11228566	68735849	+	C/T
rs11228567	68736126	+	A/G
rs7937094	68736282	+	C/T
rs11228568	68736438	+	G/T
rs11228569	68736819	+	C/T
rs4620729	68736911	+	A/C
rs11821008	68737211	+	A/G
rs11825791	68737337	+	C/G
rs11825796	68737364	+	A/G
rs4930668	68737404	+	G/T
rs10896447	68737451	+	A/C
rs4265599	68737642	+	A/T
rs12275055	68737935	+	A/G
rs4268514	68738060	+	C/G
rs28613836	68738536	+	C/T
rs9665814	68738604	+	C/T
rs4930669	68738956	+	C/T
rs4451736	68739279	+	A/G
rs5792471	68739686	+	—/C
rs4988608	68739767	+	A/G
rs4988607	68739830	+	G/T
rs12278923	68740137	+	A/C
rs7939803	68740276	+	C/T
rs10792032	68741178	+	A/G
rs12294067	68741228	+	A/G
rs11421935	68741320	+	—/G
rs11228570	68741410	+	C/T

TABLE 5-continued

Polymorphic markers within the C11 region, between position 68,709,630 and 68,782,375 in NCBI Build 36. Shown is marker ID (rs-names), position in Build 36, strand and polymorphism type, where (—/N), N being any one nucleotide, or a plurality of nucleotides, corresponding to an insertion/deletion polymorphism (i.e. either the nucleotide(s) is present or not).

Marker ID	Position Build 36	Strand	Polymorphism
rs11228571	68741445	+	C/T
rs11351679	68742057	+	—/T
rs7929962	68742159	+	C/T
rs12282709	68742244	+	A/C
rs28686842	68742981	+	C/G
rs12790802	68743071	+	A/C
rs11824985	68743246	+	A/G
rs12785252	68743916	+	A/C
rs12785424	68743958	+	A/C
rs7941085	68744228	+	G/T
rs11228572	68744280	+	A/G
rs7119440	68744363	+	A/G
rs35024453	68744479	+	—/T
rs7119681	68744563	+	A/G
rs7945227	68745639	+	A/G
rs10792033	68745774	+	A/G
rs28706904	68746828	+	C/T
rs35911114	68746864	+	—/A
rs7121816	68746871	+	G/T
rs34326593	68746958	+	—/C
rs7109672	68747686	+	A/G
rs12270972	68748240	+	A/G
rs10896448	68748325	+	C/G
rs34655741	68748385	+	—/T
rs35960410	68748742	+	—/A
rs12795301	68748861	+	A/C
rs11228573	68749659	+	G/T
rs11228574	68750098	+	A/T
rs35007842	68750196	+	—/G
rs7122190	68750364	+	C/T
rs6591374	68750408	+	A/G
rs28367011	68750751	+	C/T
rs36082692	68751072	+	—/G
rs7931342	68751073	+	G/T
rs10896449	68751243	+	A/G
rs10750845	68751541	+	A/G
rs35730578	68751818	+	—/TG
rs11228575	68751854	+	A/G
rs12365199	68751856	+	A/G
rs11228576	68752122	+	A/G
rs7130881	68752534	+	A/G
rs12362678	68752746	+	C/G
rs11603219	68753019	+	A/G
rs9787877	68753085	+	C/T
rs11603288	68753358	+	A/G
rs11228577	68753390	+	C/T
rs4644650	68754694	+	C/T
rs5792472	68754765	+	—/G
rs4569015	68754981	+	C/T
rs7950547	68755364	+	C/T
rs7935842	68755540	+	G/T
rs4576823	68755685	+	A/G
rs35572423	68755750	+	—/A
rs7931312	68757543	+	A/G
rs34699416	68757796	+	—/C
rs4930670	68757828	+	C/T
rs11605287	68758302	+	G/T
rs11228579	68758793	+	G/T
rs11228580	68758918	+	C/T
rs7925434	68759208	+	A/T
rs7939151	68759472	+	A/G
rs7939250	68759526	+	A/G
rs7118074	68759999	+	G/T
rs12788188	68760157	+	A/T
rs7106762	68760282	+	C/T
rs34000592	68760510	+	—/T
rs12417087	68760555	+	A/T
rs11228581	68760586	+	C/T
rs9667638	68760915	+	A/T
rs28852414	68761492	+	A/G

TABLE 5-continued

Polymorphic markers within the C11 region, between position 68,709,630 and 68,782,375 in NCBI Build 36. Shown is marker ID (rs-names), position in Build 36, strand and polymorphism type, where (—/N), N being any one nucleotide, or a plurality of nucleotides, corresponding to an insertion/deletion polymorphism (i.e. either the nucleotide(s) is present or not).

Marker ID	Position Build 36	Strand	Polymorphism
rs28876082	68761493	+	G/T
rs7947353	68761559	+	A/G
rs7947298	68761677	+	A/C
rs11826508	68762658	+	A/G
rs34384086	68763007	+	—/C
rs36091743	68763507	+	—/T
rs11228582	68763813	+	A/T
rs7104671	68763950	+	C/G
rs12802068	68764310	+	A/G
rs12802553	68764311	+	A/G
rs36101702	68764356	+	—/TT
rs10896450	68764690	+	A/G
rs12808564	68765268	+	A/G
rs11228583	68765690	+	G/T
rs11228584	68766043	+	A/G
rs10560769	68766333	+	—/TT
rs12293259	68766814	+	G/T
rs12799883	68767227	+	G/T
rs4451737	68767444	+	C/T
rs3925012	68767493	+	C/T
rs4131929	68768714	−	C/T
rs12270641	68768820	+	A/T
rs35310215	68769540	+	—/G
rs35836017	68769588	+	—/C
rs34255287	68769711	+	A/G
rs7127508	68770593	+	C/T
rs7111780	68770972	+	A/G
rs7111993	68771116	+	A/G
rs7112311	68771118	+	A/G
rs11603876	68771837	+	A/T
rs12282656	68772304	+	A/G
rs7119988	68772447	+	A/G
rs36031129	68772686	+	—/CC
rs11404080	68773007	+	—/T
rs35921293	68773009	+	—/T
rs10896451	68773469	+	A/C
rs34887827	68774015	+	C/T
rs12420858	68774110	+	C/G
rs11228585	68774254	+	C/T
rs10530250	68774509	+	(LARGE DELETION)/—
rs11228586	68774667	+	C/T
rs11228587	68774847	+	A/G
rs4930671	68774950	+	A/G
rs10896452	68775074	+	C/T
rs11606813	68775164	+	C/T
rs12225965	68775407	+	A/G
rs34717487	68775561	+	G/T
rs4930672	68775807	+	A/G
rs12293276	68775830	+	A/G
rs7118966	68775848	+	C/T
rs7102758	68775981	+	A/G
rs12421619	68775992	+	C/T
rs35400111	68776233	+	—/G
rs11228588	68776545	+	A/G
rs34223044	68776551	+	—/C
rs11828682	68776692	+	A/G
rs7118204	68777260	+	A/G
rs12806580	68777418	+	C/T
rs35349840	68777566	+	—/G
rs10896453	68777614	+	A/G
rs10792034	68777793	+	C/T
rs4531476	68778231	+	C/G
rs11228589	68778253	+	A/G
rs11228590	68778283	+	C/T
rs11228591	68779388	+	A/C
rs35087861	68779558	+	—/G
rs11228593	68779604	+	A/G
rs11228594	68779663	+	A/G
rs11228595	68779946	+	C/T

TABLE 5-continued

Polymorphic markers within the C11 region, between position 68,709,630 and 68,782,375 in NCBI Build 36. Shown is marker ID (rs-names), position in Build 36, strand and polymorphism type, where (—/N), N being any one nucleotide, or a plurality of nucleotides, corresponding to an insertion/deletion polymorphism (i.e. either the nucleotide(s) is present or not).

Marker ID	Position Build 36	Strand	Polymorphism
rs7127913	68780032	+	C/G
rs10736673	68780073	+	C/T
rs11228596	68780341	+	A/G
rs11228597	68780850	+	A/G
rs36061232	68781372	+	—/A
rs11602505	68781617	+	C/G
rs7928306	68781639	+	C/T
rs11228598	68781757	+	A/G
rs7121952	68781886	+	C/T
rs12792211	68782129	+	A/G
rs7122303	68782158	+	C/T
rs3884627	68782375	−	A/C

TABLE 6

Polymorphic markers within the C06 region, between position 79,300,773 and 79,917,888 in NCBI Build 36. Shown is marker ID (rs-names), position in Build 36, strand and polymorphism type, where (—/N), N being any nucleotide or a plurality of nucleotides, corresponding to an insertion/deletion polymorphism (i.e. either the nucleotide(s) is present or not, as indicated).

Marker ID	Position Build 36	Strand	Polymorphism
rs611737	79300773	+	A/T
rs626819	79301359	+	A/G
rs6910813	79302376	+	C/T
rs12214422	79302660	+	A/G
rs644560	79303061	+	C/T
rs9352604	79303344	+	A/G
rs9448457	79303808	+	C/T
rs686492	79305307	+	C/T
rs9448458	79305343	+	A/G
rs6929235	79305516	+	C/T
rs34452249	79305637	+	—/A
rs7749430	79305957	+	A/G
rs817878	79306182	+	C/T
rs9443588	79306226	+	A/G
rs9448459	79306228	+	A/G
rs7749697	79306342	+	C/T
rs768590	79306749	+	C/T
rs9448460	79306888	+	A/G
rs35921129	79307666	+	—/G
rs586228	79308383	+	C/T
rs34460368	79308541	+	—/C
rs680095	79309251	+	G/T
rs36120289	79309395	+	—/T
rs681322	79309441	+	A/G
rs681802	79309548	+	A/C
rs36181646	79310146	+	—/T
rs7742933	79310346	+	C/G
rs7742862	79310526	+	A/T
rs34040490	79311019	+	—/A
rs9359329	79311380	+	C/T
rs9294118	79311509	+	A/T
rs9341737	79311928	+	G/T
rs9443589	79312030	+	C/G
rs1506767	79312288	+	A/C
rs9448462	79312500	+	A/G
rs9359330	79312505	+	C/T
rs817881	79312760	+	A/T
rs9448463	79312774	+	A/G
rs817882	79312776	+	A/G
rs4321794	79312812	+	A/G
rs817883	79313522	+	C/G
rs9448464	79313952	+	A/C

TABLE 6-continued

Polymorphic markers within the C06 region, between position 79,300,773 and 79,917,888 in NCBI Build 36. Shown is marker ID (rs-names), position in Build 36, strand and polymorphism type, where (—/N), N being any nucleotide or a plurality of nucleotides, corresponding to an insertion/deletion polymorphism (i.e. either the nucleotide(s) is present or not, as indicated).

Marker ID	Position Build 36	Strand	Polymorphism
rs590624	79314042	–	A/C
rs9448465	79314256	+	A/C
rs34720156	79314273	+	—/C/T
rs9443590	79314631	+	A/G
rs587503	79314716	–	C/G
rs9448466	79315160	+	A/G
rs682852	79315205	+	A/T
rs9443591	79315537	+	C/T
rs12183583	79315477	+	C/T
rs12202264	79315943	+	A/G
rs9443592	79316009	+	A/G
rs35257893	79316335	+	—/C
rs666982	79316431	+	C/T
rs9443593	79316432	+	C/T
rs34323328	79316810	+	—/T
rs654652	79316879	+	G/T
rs12528215	79316955	+	A/C
rs34348581	79317371	+	—/A
rs652356	79317426	+	A/T
rs651900	79317529	–	G/T
rs651894	79317535	–	G/T
rs10565029	79317635	+	—/AAA
rs10590702	79317656	+	—/AAA
rs17823349	79318539	+	C/T
rs35611717	79319004	+	—/TTT
rs2024994	79319262	+	C/T
rs34242911	79319291	+	—/A
rs6932288	79319758	+	G/T
rs16890129	79319993	+	C/T
rs600913	79320040	+	C/T
rs1625514	79320259	+	C/T
rs10611862	79320291	+	—/AC
rs10695566	79320376	+	—/C/T/TA
rs28652972	79320377	+	C/T
rs34108696	79320377	+	—/TA
rs13214614	79320385	+	C/G
rs13214617	79320392	+	A/G
rs817886	79320395	+	—/A/G/GT
rs28736801	79320394	+	A/G
rs13214437	79320413	+	C/T
rs13214632	79320425	+	C/G
rs12200116	79320434	+	A/G
rs12213654	79320441	+	C/T
rs13200111	79320447	+	C/T
rs9341738	79320646	+	G/T
rs1616969	79320658	–	A/C
rs12215356	79320880	+	A/G
rs3063781	79321086	+	—/GATA
rs616011	79321162	+	C/T
rs685093	79321296	+	C/T
rs1321599	79321507	+	C/T
rs12195790	79321512	+	A/T
rs12215690	79321527	+	A/G
rs9448467	79321532	+	A/G
rs10214428	79321604	+	A/G
rs5877614	79321661	+	—/ATGT
rs35273466	79321666	+	—/TGTA
rs10214574	79321924	+	C/T
rs12203729	79321949	+	A/G
rs653092	79322088	–	A/G
rs34332845	79322089	+	CA/TG
rs653091	79322089	–	C/T
rs12190592	79322474	+	C/T
rs669241	79322487	–	C/T
rs13328234	79322502	+	C/T
rs11963866	79322524	+	A/T
rs668305	79322704	–	A/G
rs9448468	79322719	+	C/T
rs656825	79322983	–	A/T
rs656806	79322991	–	C/T

TABLE 6-continued

Polymorphic markers within the C06 region, between position 79,300,773 and 79,917,888 in NCBI Build 36. Shown is marker ID (rs-names), position in Build 36, strand and polymorphism type, where (—/N), N being any nucleotide or a plurality of nucleotides, corresponding to an insertion/deletion polymorphism (i.e. either the nucleotide(s) is present or not, as indicated).

Marker ID	Position Build 36	Strand	Polymorphism
rs656767	79323027	–	C/T
rs636717	79323460	–	C/T
rs623155	79324200	–	A/G
rs1588045	79324435	–	A/G
rs1588044	79324438	–	A/G
rs12154026	79324811	+	C/T
rs36029617	79324861	+	A/C
rs627261	79324993	–	A/T
rs9448469	79325158	+	A/T
rs12196214	79325431	+	C/T
rs625065	79325534	+	C/T
rs625051	79325550	+	G/T
rs623658	79325869	–	A/G
rs611493	79326235	+	A/G
rs34644016	79326358	+	—/C
rs7762380	79326371	+	C/T
rs2063044	79327042	–	A/G
rs2057299	79327290	+	C/T
rs685245	79327502	+	G/T
rs9443594	79327549	+	A/G
rs594889	79327616	+	—/A/T
rs2321446	79328223	+	C/G
rs2321447	79328224	+	C/T
rs9294119	79328300	+	A/G
rs12200457	79328690	+	G/T
rs675860	79328980	–	C/T
rs1395451	79329158	–	A/C
rs5877615	79329487	+	—/AG
rs33932619	79329488	+	—/AG
rs2307940	79329492	–	—/TC
rs9448471	79329660	+	C/T
rs627504	79329799	–	C/T
rs817874	79329815	–	A/T
rs34927882	79330116	+	—/C
rs4532413	79330118	+	A/G
rs7755570	79330301	+	A/G
rs624930	79330391	–	A/G
rs7755650	79330536	+	A/C
rs11321290	79330606	+	—/A
rs4055943	79330613	+	—/AA
rs5877616	79330615	+	—/A/AA
rs623900	79330662	+	A/C
rs35720273	79331059	+	A/T
rs9448472	79331128	+	C/T
rs1354783	79331316	–	A/G
rs9448473	79332278	+	A/C
rs9448474	79332375	+	A/G
rs9448475	79332618	+	C/T
rs10485132	79333000	–	A/G
rs9448476	79333023	+	G/T
rs9361409	79333075	+	C/T
rs6936674	79333218	+	A/C
rs599356	79333269	+	C/G
rs9448477	79333362	+	C/G
rs35610189	79333362	+	—/C
rs9350762	79333552	+	C/T
rs35356866	79333742	+	—/A
rs9443595	79333782	+	C/T
rs817873	79333940	+	A/C
rs34056090	79334129	+	—/G
rs35568407	79334141	+	—/C
rs35329543	79334333	+	—/G
rs1180729	79334524	+	A/T
rs12203331	79334532	+	C/T
rs11966608	79335281	+	C/T
rs12527974	79335652	+	C/T
rs2321448	79335824	+	A/C
rs4357091	79335896	+	A/T
rs35401847	79336555	+	—/A
rs34962042	79336668	+	—/G

TABLE 6-continued

Polymorphic markers within the C06 region, between position 79,300,773 and 79,917,888 in NCBI Build 36. Shown is marker ID (rs-names), position in Build 36, strand and polymorphism type, where (—/N), N being any nucleotide or a plurality of nucleotides, corresponding to an insertion/deletion polymorphism (i.e. either the nucleotide(s) is present or not, as indicated).

Marker ID	Position Build 36	Strand	Polymorphism
rs34243415	79336793	+	—/C
rs660115	79336811	–	A/G
rs665915	79336879	+	C/T
rs2321449	79337577	+	A/C
rs10214706	79337707	+	A/G
rs645217	79337828	–	C/T
rs9448478	79338056	+	A/T
rs1180712	79339059	+	G/T
rs34586728	79339119	+	A/C
rs34371761	79339519	+	—/A
rs5877617	79339832	+	—/C
rs12202205	79340216	+	C/T
rs2022199	79340391	–	C/T
rs5877618	79340404	+	—/A
rs34256059	79340405	+	—/A
rs5877619	79340411	+	—/A
rs35771902	79340412	+	—/A
rs2022198	79340494	–	C/T
rs615980	79340588	+	C/T
rs35269485	79340618	+	—/A
rs2022197	79340630	–	C/T
rs616526	79340734	+	A/G
rs547472	79341083	+	C/T
rs4706714	79341084	+	A/C
rs9448479	79341414	+	C/T
rs671940	79342180	–	C/T
rs2321450	79342370	+	C/G
rs662430	79342674	+	C/T
rs12214043	79342882	+	A/T
rs34757416	79342885	+	—/CA
rs1853111	79342888	+	C/T
rs34922104	79342890	+	—/TT
rs12207739	79342893	+	A/T
rs28643317	79342897	+	A/T
rs28498695	79342903	+	A/T
rs28394665	79342909	+	A/T
rs10455117	79342926	+	A/T
rs474764	79342934	+	G/T
rs28436215	79342992	+	A/C
rs10455118	79343162	+	A/C
rs28662236	79343365	+	A/G
rs34757274	79343581	+	—/C
rs654628	79343805	–	C/T
rs11755496	79343990	+	C/G
rs528850	79344165	+	C/G
rs16890160	79344345	+	C/T
rs1033691	79344906	+	C/T
rs1964131	79345300	+	—/A/G
rs1964132	79345301	+	A/G
rs627292	79345308	–	A/G
rs627289	79345314	–	C/G
rs7767332	79345618	+	A/T
rs9448480	79345810	+	C/T
rs605822	79345825	+	A/G
rs605697	79345910	+	A/G
rs605264	79346003	+	C/T
rs603964	79346271	–	A/G
rs612489	79346309	–	G/T
rs484582	79346824	+	G/T
rs35610422	79346949	+	—/G
rs35763342	79347019	+	—/T
rs9448481	79347164	+	C/G
rs9448482	79347421	+	C/T
rs597283	79347449	–	C/G
rs596810	79347562	–	C/T
rs596337	79347676	–	C/T
rs34739094	79347711	+	—/G
rs9448484	79347965	+	C/T
rs655566	79348564	–	A/G
rs581416	79348610	–	C/G

TABLE 6-continued

Polymorphic markers within the C06 region, between position 79,300,773 and 79,917,888 in NCBI Build 36. Shown is marker ID (rs-names), position in Build 36, strand and polymorphism type, where (—/N), N being any nucleotide or a plurality of nucleotides, corresponding to an insertion/deletion polymorphism (i.e. either the nucleotide(s) is present or not, as indicated).

Marker ID	Position Build 36	Strand	Polymorphism
rs689389	79348661	–	A/G
rs846453	79348794	–	C/G
rs846452	79348887	–	A/G
rs11755342	79349385	+	C/T
rs34223893	79349579	+	—/G
rs674105	79349688	–	A/G
rs9448485	79350112	+	A/G
rs9443596	79350335	+	A/G
rs12181074	79350315	+	A/G
rs17225876	79350594	+	C/T
rs11751885	79350686	+	A/G
rs7746355	79351241	+	A/C
rs7746614	79351279	+	C/T
rs34541692	79351399	+	—/A
rs699174	79351582	–	A/G
rs9448486	79351645	+	A/C
rs699175	79351931	–	C/T
rs699176	79352012	–	A/G
rs236863	79352234	–	A/G
rs12207987	79352301	+	G/T
rs13201882	79352366	+	A/G
rs9448487	79352398	+	G/T
rs9443597	79352413	+	C/T
rs9448488	79352736	+	C/T
rs9443598	79352745	+	C/T
rs9448489	79352746	+	A/G
rs3967379	79353019	+	C/T
rs236864	79353190	+	C/G
rs12209919	79353401	+	A/G
rs12209974	79353466	+	C/G
rs236865	79353475	+	C/G
rs9443599	79354012	+	A/G
rs236866	79354277	–	A/G
rs1137258	79354328	+	A/G
rs9448490	79354814	+	A/C
rs17332393	79355181	+	C/T
rs11759337	79355380	+	A/G
rs236867	79355383	+	C/T
rs9448491	79355466	+	A/G
rs236868	79355488	+	G/T
rs236869	79355706	+	C/T
rs9443600	79356397	+	G/T
rs236870	79356774	+	C/T
rs236871	79356925	+	C/T
rs16890184	79357098	+	C/T
rs9443601	79357369	+	A/G
rs9448492	79357532	+	C/T
rs236872	79358008	–	C/T
rs9448493	79358214	+	C/T
rs7776020	79358245	+	C/T
rs236873	79358580	–	A/G
rs11753657	79358850	+	A/C
rs34736990	79359228	+	—/T
rs11461852	79359513	+	—/T
rs9448495	79359564	+	C/T
rs9448496	79359649	+	A/G
rs9448497	79360057	+	C/T
rs236874	79360347	+	A/G
rs9443602	79360653	+	C/T
rs192101	79360986	+	A/G
rs35198424	79361056	+	—/A
rs236875	79361403	+	A/C
rs11366261	79361558	+	—/A
rs236876	79362007	+	C/G
rs12203300	79362176	+	A/T
rs236877	79362203	+	A/G
rs9448498	79362482	+	A/G
rs11756326	79362950	+	A/G
rs9448499	79363791	+	A/C
rs9448500	79363928	+	A/T

TABLE 6-continued

Polymorphic markers within the C06 region, between position 79,300,773 and 79,917,888 in NCBI Build 36. Shown is marker ID (rs-names), position in Build 36, strand and polymorphism type, where (—/N), N being any nucleotide or a plurality of nucleotides, corresponding to an insertion/deletion polymorphism (i.e. either the nucleotide(s) is present or not, as indicated).

Marker ID	Position Build 36	Strand	Polymorphism
rs10485131	79364083	–	C/T
rs7770444	79364354	+	C/T
rs11757555	79364553	+	A/C
rs236878	79364707	–	G/T
rs910955	79364822	+	A/G
rs70478	79364899	+	C/T
rs70480	79365324	+	A/G
rs5877620	79365398	+	—/T
rs731449	79365401	–	A/G/T
rs35967646	79365405	+	—/A
rs9294120	79365528	+	C/T
rs35822945	79365869	+	—/T
rs9343779	79365908	+	A/G
rs699178	79366002	+	C/T
rs2750022	79366008	+	A/C
rs699179	79366252	+	A/G
rs699180	79366351	+	C/T
rs9448502	79366447	+	A/C
rs35286686	79366524	+	—/T
rs9448503	79366694	+	C/G
rs35383112	79367223	+	—/A
rs699181	79367333	+	C/T
rs7356833	79367828	+	A/G
rs7356834	79367837	+	A/G
rs34785800	79367950	+	—/T
rs7356836	79367968	+	A/G
rs5877621	79368047	+	—/C
rs7356840	79368100	+	A/G
rs7356843	79368150	+	G/T
rs9294121	79368152	+	G/T
rs7356844	79368157	+	A/G
rs236879	79368578	–	A/C
rs34335044	79368627	+	—/C
rs9448504	79369400	+	C/G
rs9448505	79369555	+	C/T
rs9448506	79369591	+	A/T
rs9359332	79369685	+	G/T
rs236880	79369811	–	A/T
rs9448507	79370086	+	A/G
rs9448508	79370320	+	A/G
rs9443603	79370631	+	A/C
rs236881	79370661	–	C/G
rs9448509	79371433	+	A/G
rs11964133	79371604	+	C/T
rs35268570	79371715	+	—/G
rs498037	79371989	–	A/G
rs1570075	79372076	+	A/C
rs1567097	79372765	–	A/T
rs1567096	79372799	–	A/G
rs236882	79372832	+	A/G
rs12200556	79372896	+	C/T
rs10806133	79372949	+	C/T
rs35217057	79373409	+	—/TGGA
rs717364	79374159	+	A/G
rs11757996	79374370	+	C/T
rs1995650	79375007	–	C/T
rs500391	79375065	+	A/G
rs596057	79375070	–	A/C
rs34948829	79375296	+	G/T
rs2021855	79375397	–	A/T
rs17226851	79375471	+	A/G
rs984157	79375681	–	C/T
rs1395447	79376010	–	C/T
rs9361411	79376022	+	A/G
rs236883	79376130	–	A/C
rs236884	79376244	+	C/G
rs9448510	79376314	+	C/T
rs12197910	79376609	+	C/T
rs2307943	79376998	+	—/AA
rs10539915	79376999	+	—/AA

TABLE 6-continued

Polymorphic markers within the C06 region, between position 79,300,773 and 79,917,888 in NCBI Build 36. Shown is marker ID (rs-names), position in Build 36, strand and polymorphism type, where (—/N), N being any nucleotide or a plurality of nucleotides, corresponding to an insertion/deletion polymorphism (i.e. either the nucleotide(s) is present or not, as indicated).

Marker ID	Position Build 36	Strand	Polymorphism
rs4551135	79377021	+	G/T
rs10943547	79378077	+	A/G
rs236885	79378204	+	A/G
rs236886	79378253	+	A/C
rs10943548	79378357	+	C/T
rs35488554	79378364	+	A/C
rs236887	79378393	–	A/T
rs16890218	79378495	+	G/T
rs236888	79378960	+	C/T
rs236889	79379130	–	A/G
rs16890224	79379278	+	A/T
rs1407102	79379719	+	C/T
rs17825291	79379916	+	C/T
rs34286917	79380641	+	—/A
rs1012026	79381031	+	A/G
rs236890	79381351	+	A/C
rs236891	79381414	+	C/T
rs1012027	79381592	+	C/T
rs34331673	79382209	+	—/G
rs9448511	79382811	+	C/T
rs17227220	79382837	+	A/G
rs16890230	79382886	+	A/T
rs236892	79382966	–	C/T
rs12189761	79382972	+	A/T
rs12209692	79383101	+	A/G
rs1395446	79383114	–	A/C
rs34707756	79383315	+	—/A
rs16890234	79383336	+	A/G
rs2021251	79383492	–	C/G
rs10943549	79383908	+	C/T
rs699182	79384047	+	G/T
rs3035341	79384211	+	—/AAAAA
rs34681522	79384257	+	—/T
rs1186428	79384269	–	A/G
rs2022521	79384282	–	G/T
rs817889	79384562	–	A/G
rs6931841	79384660	+	C/T
rs6932494	79384868	+	A/G
rs9359333	79384897	+	C/T
rs12213548	79385071	+	G/T
rs12525083	79385670	+	C/T
rs11970272	79385707	+	C/T
rs10455349	79387663	+	C/G
rs2063045	79388058	–	A/G
rs11757737	79388316	+	A/C
rs12197137	79388567	+	A/G
rs9448512	79389055	+	A/T
rs35065237	79389616	+	—/T
rs10630134	79389747	+	—/TA
rs34896371	79389748	+	—/TA
rs34598417	79389756	+	—/AT
rs236859	79389835	–	C/T
rs6454064	79389958	+	G/T
rs6454065	79390047	+	G/T
rs41501448	79390057	+	C/T
rs10640580	79390177	+	—/CACA
rs34677786	79390178	+	—/CACA
rs10565820	79390187	+	—/CA
rs10542873	79390189	+	—/CA
rs10536481	79390190	+	—/AC
rs6454066	79390202	+	C/T
rs6454067	79390311	+	C/T
rs1567095	79390707	–	C/T
rs1570001	79390750	+	C/T
rs236860	79390814	–	C/T
rs236861	79390866	+	C/T
rs12530012	79390899	+	C/T
rs9443604	79391001	+	C/G
rs12530067	79391157	+	C/T
rs12530068	79391178	+	C/T

TABLE 6-continued

Polymorphic markers within the C06 region, between position 79,300,773 and 79,917,888 in NCBI Build 36. Shown is marker ID (rs-names), position in Build 36, strand and polymorphism type, where (—/N), N being any nucleotide or a plurality of nucleotides, corresponding to an insertion/deletion polymorphism (i.e. either the nucleotide(s) is present or not, as indicated).

Marker ID	Position Build 36	Strand	Polymorphism
rs12530072	79391243	+	C/T
rs4286729	79391508	+	C/T
rs236862	79391691	–	A/G
rs35710435	79391916	+	—/G
rs5877622	79391938	+	—/G
rs12190115	79392540	+	A/G
rs699183	79392730	+	A/G
rs34692849	79392774	+	—/T
rs10943550	79392824	+	G/T
rs10943551	79393059	+	G/T
rs11413951	79393172	+	—/A
rs35198419	79393180	+	—/A
rs35839290	79393308	+	C/T
rs11752300	79393726	+	C/T
rs12200526	79393754	+	C/T
rs12193597	79393898	+	A/G
rs12524686	79394235	+	C/G
rs35481326	79394369	+	—/C
rs659108	79395159	–	G/T
rs7775572	79395255	+	C/T
rs7755578	79395265	+	A/G
rs12195709	79395315	+	A/G
rs7775782	79395445	+	A/G
rs7755682	79395539	+	C/T
rs12210711	79396008	+	A/G
rs236853	79396185	–	A/G
rs34570358	79396388	+	—/T
rs35919105	79396567	+	C/T
rs12530353	79396617	+	A/G
rs6940529	79396666	+	A/C
rs12530368	79396668	+	A/G
rs6940555	79396714	+	A/C
rs6941006	79396789	+	A/G
rs6920658	79396993	+	C/T
rs11755479	79397125	+	A/T
rs12665819	79397185	+	A/G
rs9448513	79397377	+	A/G
rs12191138	79397842	+	C/G
rs10615883	79397992	+	—/TC
rs10563095	79397998	+	—/TC
rs236854	79398400	+	G/T
rs236855	79398610	–	A/G
rs9443605	79398716	+	C/T
rs497885	79398799	+	G/T
rs2321764	79399237	+	C/G
rs5018093	79399607	+	C/T
rs12201840	79399748	+	C/T
rs9448514	79399769	+	A/C
rs34938165	79400028	+	—/GA
rs35821097	79400053	+	—/C
rs7774339	79400463	+	C/T
rs236856	79400485	+	A/G
rs236857	79401130	+	C/T
rs9448515	79401281	+	A/G
rs236858	79401284	+	C/T
rs699184	79401788	–	A/C
rs512778	79401865	+	A/G
rs9361413	79401968	+	A/G
rs3220157	79402127	+	(CA)24/25/26/28/29/30/31/33
rs36212818	79402095	+	—/CACACA
rs5877623	79402087	+	—/CACACACA
rs33979908	79402121	+	—/CACACACACA

TABLE 6-continued

Polymorphic markers within the C06 region, between position 79,300,773 and 79,917,888 in NCBI Build 36. Shown is marker ID (rs-names), position in Build 36, strand and polymorphism type, where (—/N), N being any nucleotide or a plurality of nucleotides, corresponding to an insertion/deletion polymorphism (i.e. either the nucleotide(s) is present or not, as indicated).

Marker ID	Position Build 36	Strand	Polymorphism
rs9361414	79402167	+	G/T
rs5877624	79402681	+	—/G
rs541337	79402708	+	A/G
rs2321765	79402846	+	C/G
rs699185	79403177	+	A/G
rs236848	79403803	+	A/G
rs11965655	79403862	+	A/G
rs236849	79403916	–	A/G
rs10701196	79403945	+	—/AA
rs35128239	79404539	+	—/C
rs236850	79405375	+	A/C
rs6904390	79405458	+	A/T
rs6909051	79405613	+	C/T
rs12206138	79405708	+	C/T
rs34566789	79405761	+	—/C
rs6909339	79405768	+	C/G
rs6909644	79405797	+	A/G
rs6909663	79405829	+	G/T
rs6910018	79405963	+	A/G
rs171050	79406031	+	A/G
rs236851	79406471	+	A/G
rs236852	79406611	+	A/C
rs35683036	79406788	+	—/C
rs7763429	79407488	+	A/G
rs28797508	79407906	+	A/T
rs34457432	79407905	+	—/A
rs28845244	79407909	+	A/T
rs11967330	79408002	+	G/T
rs9766611	79408248	+	C/G
rs9767153	79408285	+	C/T
rs11967401	79408313	+	G/T
rs34710160	79408331	+	—/T
rs9767594	79408340	+	A/G
rs9767160	79408362	+	C/T
rs9766716	79408582	+	C/T
rs9766717	79408597	+	C/T
rs9767724	79408721	+	A/G
rs9767248	79408857	+	C/T
rs11755206	79408909	+	C/T
rs11755256	79408948	+	G/T
rs663954	79408987	+	C/G
rs35768463	79409014	+	C/G
rs2202590	79409231	–	A/C
rs34750624	79409440	+	—/AACA
rs125272367	9409757	+	C/G
rs7740665	79410184	+	C/T
rs4547970	79410315	+	A/G
rs34273395	79410347	+	—/T
rs10455350	79410646	+	A/G
rs583747	79411314	–	A/T
rs10455351	79411324	+	G/T
rs34113682	79411805	+	—/C
rs6936649	79411878	+	A/T
rs6913931	79412046	+	C/T
rs9343780	79412054	+	C/T
rs1172263	79412098	–	A/T
rs7751786	79412433	+	A/T
rs1069028	79412764	–	A/C
rs4706716	79412775	+	G/T
rs7738229	79412794	+	A/T
rs7756398	79412809	+	A/C
rs7756411	79412884	+	A/C
rs7756809	79412901	+	A/G
rs7756442	79412946	+	A/G
rs34345701	79412986	+	G/T
rs9448517	79413089	+	G/T
rs11753268	79413379	+	A/G
rs2202589	79413464	–	A/G
rs2202588	79413475	–	C/T
rs11758439	79413558	+	C/T

TABLE 6-continued

Polymorphic markers within the C06 region, between position 79,300,773 and 79,917,888 in NCBI Build 36. Shown is marker ID (rs-names), position in Build 36, strand and polymorphism type, where (—/N), N being any nucleotide or a plurality of nucleotides, corresponding to an insertion/deletion polymorphism (i.e. either the nucleotide(s) is present or not, as indicated).

Marker ID	Position Build 36	Strand	Polymorphism
rs7761199	79413617	+	A/G
rs11753781	79413684	+	A/C
rs10455119	79413685	+	A/G
rs4530796	79414858	+	—/T
rs9448518	79414973	+	A/G
rs9443606	79415015	+	C/G
rs9443607	79415153	+	C/T
rs13213955	79415197	+	A/T
rs9350767	79415702	+	A/C
rs7772851	79416038	+	C/T
rs6454070	79416268	+	A/C
rs7773660	79416279	+	A/G
rs7773550	79416449	+	A/G
rs9448519	79416456	+	C/G
rs7773732	79416491	+	A/C
rs9448520	79416508	+	A/G
rs9361418	79416542	+	C/T
rs7774017	79416543	+	A/G
rs34978259	79416789	+	—/C
rs13199250	79416845	+	A/C
rs12528155	79417363	+	A/G
rs12528140	79417430	+	A/C
rs12524711	79417477	+	A/G
rs12528168	79417483	+	A/G
rs12529963	79417494	+	A/T
rs12525058	79417555	+	A/T
rs12528513	79417619	+	C/G
rs35973698	79417626	+	—/A
rs9448521	79418135	+	C/T
rs13204264	79418289	+	A/C
rs13204489	79418306	+	G/T
rs13220434	79418337	+	C/T
rs13204504	79418338	+	A/G
rs13204411	79418403	+	A/C
rs10943555	79418521	+	A/G
rs12182690	79418612	+	C/T
rs11758282	79418731	+	A/G
rs10943556	79418749	+	A/C
rs11758301	79418757	+	G/T
rs12182714	79418795	+	A/C
rs10943557	79418878	+	G/T
rs10943558	79418957	+	A/G
rs10943559	79418973	+	A/C
rs12529060	79419023	+	G/T
rs12529083	79419172	+	A/G
rs12529066	79419210	+	C/T
rs13208861	79419298	+	C/G
rs35723058	79419309	+	—/T
rs12524083	79419353	+	C/T
rs4481395	79420009	+	A/G
rs9359334	79420248	+	C/G
rs12662183	79420296	+	A/G
rs13202661	79421089	+	G/T
rs2321767	79421453	+	C/T
rs6921541	79421621	+	C/T
rs11750986	79422024	+	C/T
rs11755647	79422090	+	A/C
rs35959932	79422201	+	—/C
rs34291901	79422318	+	A/T
rs9343782	79422366	+	G/T
rs34044761	79424096	+	—/G
rs11399404	79424247	+	—/A
rs17234476	79425078	+	G/T
rs5877625	79425313	+	—/T
rs35681689	79425314	+	—/T
rs34020492	79425316	+	—/T
rs13220214	79425378	+	G/T
rs12210702	79426052	+	A/G
rs12525652	79426301	+	A/C
rs1938554	79426313	+	C/G

TABLE 6-continued

Polymorphic markers within the C06 region, between position 79,300,773 and 79,917,888 in NCBI Build 36. Shown is marker ID (rs-names), position in Build 36, strand and polymorphism type, where (—/N), N being any nucleotide or a plurality of nucleotides, corresponding to an insertion/deletion polymorphism (i.e. either the nucleotide(s) is present or not, as indicated).

Marker ID	Position Build 36	Strand	Polymorphism
rs12525655	79426333	+	C/T
rs35676724	79426360	+	—/T
rs12525674	79426408	+	C/T
rs12527490	79426534	+	A/T
rs36020193	79426610	+	—/T
rs12530352	79426691	+	A/G
rs12526918	79426820	+	A/G
rs12215953	79426831	+	C/T
rs2154396	79426988	+	C/T
rs10943560	79427137	+	C/T
rs35902159	79427208	+	—/AAT
rs6941828	79427531	+	C/G
rs17234622	79427610	+	A/G
rs10485130	79427659	–	A/G
rs10485129	79427902	–	C/T
rs17826325	79427930	+	C/T
rs10485128	79428165	–	A/C
rs9361420	79428649	+	A/G
rs17826379	79428843	+	A/C
rs9443608	79429038	+	A/T
rs7768733	79429515	+	C/T
rs12194701	79429556	+	A/G
rs12528303	79429558	+	A/C
rs7752431	79429626	+	C/T
rs12524924	79429653	+	C/T
rs12524949	79429719	+	A/G
rs1938555	79430010	+	A/G
rs1938556	79430133	+	A/G
rs11962962	79430380	+	C/G
rs35016983	79430502	+	—/T
rs12661567	79430711	+	C/T
rs9448524	79430774	+	C/G
rs12196899	79431241	+	A/G
rs7453195	79431988	+	G/T
rs35095504	79432065	+	C/T
rs11756592	79432239	+	C/T
rs12198749	79432255	+	C/T
rs11754162	79432324	+	A/G
rs11964250	79432345	+	C/T
rs11756635	79432372	+	C/T
rs12198976	79432495	+	C/G
rs11758823	79432516	+	A/G
rs12526451	79432811	+	A/G
rs35824053	79432979	+	—/GT
rs9361422	79434457	+	C/G
rs12527341	79434703	+	C/T
rs34470324	79434880	+	—/T
rs16890254	79435141	+	G/T
rs11751443	79435191	+	A/G
rs10943561	79435271	+	A/G
rs34358078	79435272	+	AT/GC
rs10943562	79435272	+	C/T
rs11758593	79435318	+	G/T
rs11759124	79435551	+	A/T
rs17234902	79435793	+	A/G
rs1954659	79436179	–	G/T
rs9443609	79436197	+	A/C
rs1954658	79436315	–	G/T
rs11756825	79436318	+	A/G
rs1954657	79436419	–	A/G
rs34627531	79436474	+	A/G
rs17826615	79436664	+	C/T
rs17235062	79436828	+	C/G
rs9359335	79436942	+	C/T
rs16890261	79437480	+	A/G
rs34327517	79437516	+	—/C
rs17235125	79437555	+	A/G
rs17235167	79437614	+	C/G
rs17235209	79437636	+	C/T
rs34645505	79437645	+	—/C

TABLE 6-continued

Polymorphic markers within the C06 region, between position 79,300,773 and 79,917,888 in NCBI Build 36. Shown is marker ID (rs-names), position in Build 36, strand and polymorphism type, where (—/N), N being any nucleotide or a plurality of nucleotides, corresponding to an insertion/deletion polymorphism (i.e. either the nucleotide(s) is present or not, as indicated).

Marker ID	Position Build 36	Strand	Polymorphism
rs17826801	79437741	+	A/G
rs16890263	79438616	+	C/T
rs2321768	79438791	+	A/T
rs12201253	79439572	+	G/T
rs34671943	79439692	+	—/C
rs6914850	79439950	+	C/G
rs12194506	79440009	+	A/G
rs1938553	79440281	–	A/C
rs1938552	79442027	–	C/G
rs1938551	79442188	–	A/G
rs1938550	79442759	–	G/T
rs1938549	79442785	–	C/G
rs4371819	79443838	+	A/G
rs3207577	79443876	+	G/T
rs2226283	79444234	–	C/T
rs34263174	79444643	+	—/C
rs9443610	79444913	+	C/T
rs6901727	79444923	+	A/G
rs9359337	79446035	+	C/T
rs9352610	79446117	+	A/G
rs4590226	79446611	+	C/G
rs4568410	79448079	+	A/G
rs4358581	79448365	+	A/G
rs36159891	79448536	+	—/G
rs12214797	79448885	+	A/G
rs12203087	79449566	+	C/T
rs1938548	79450052	+	A/G
rs237114	79450160	+	C/G
rs237113	79450255	+	C/T
rs9448526	79450659	+	A/G
rs9294124	79450941	+	C/T
rs237112	79451719	+	A/G
rs9443611	79451898	+	C/T
rs28510272	79452108	+	G/T
rs5877626	79452148	+	—/T
rs28715651	79452155	+	C/T
rs36084918	79452165	+	—/T
rs237111	79452657	+	A/C
rs9359338	79453470	+	C/T
rs9352611	79453687	+	C/T
rs9448528	79453785	+	C/T
rs190210	79455101	–	A/G
rs633117	79456053	+	C/T
rs36071262	79456190	+	—/T
rs578709	79456303	+	C/T
rs9448529	79456446	+	A/G
rs631308	79456494	+	C/T
rs580694	79456568	+	C/G
rs496269	79457094	–	A/G
rs10678940	79457699	+	—/AATG
rs35912544	79457700	+	—/AATG
rs35640072	79457977	+	—/C
rs639370	79458132	+	C/T
rs2307947	79458723	+	—/AAG
rs1180811	79458783	+	A/G
rs10943567	79459170	+	C/T
rs500306	79459437	+	C/T
rs621121	79459440	–	A/G
rs524008	79459763	+	A/C
rs605868	79460512	+	A/C
rs553313	79460609	+	A/G
rs605016	79460685	–	C/G
rs553545	79460686	+	A/C
rs10943568	79460926	+	G/T
rs557062	79461079	+	C/T
rs9359339	79461851	+	A/G
rs1099816	79461906	+	A/G
rs1099817	79462027	+	A/C
rs11760142	79462156	+	A/G
rs36155678	79462155	+	—/A

TABLE 6-continued

Polymorphic markers within the C06 region, between position 79,300,773 and 79,917,888 in NCBI Build 36. Shown is marker ID (rs-names), position in Build 36, strand and polymorphism type, where (—/N), N being any nucleotide or a plurality of nucleotides, corresponding to an insertion/deletion polymorphism (i.e. either the nucleotide(s) is present or not, as indicated).

Marker ID	Position Build 36	Strand	Polymorphism
rs237117	79462475	–	C/T
rs34503722	79462774	+	—/T
rs36003173	79463000	+	CAT/TGG
rs9352612	79463306	+	C/T
rs35073587	79463953	+	—/T
rs237116	79465318	–	A/G
rs13219002	79465340	+	G/T
rs36187425	79465396	+	—/T
rs4116296	79465874	+	A/C
rs9688758	79465988	+	C/T
rs36167084	79466143	+	—/A
rs11759842	79466549	+	G/T
rs237115	79467111	+	A/G
rs11751263	79467773	+	C/T
rs10591157	79468622	+	—/AGG
rs1180810	79468743	+	C/G
rs12192387	79468754	+	C/T
rs9361423	79468991	+	G/T
rs13197296	79469397	+	A/C
rs13197299	79469399	+	A/C
rs13197312	79469415	+	A/T
rs13197402	79469451	+	A/C
rs13197429	79469504	+	A/C
rs13197432	79469507	+	A/C
rs237110	79469629	–	C/G
rs35083334	79470193	+	—/T
rs34384472	79470458	+	—/C
rs35723904	79470956	+	—/T
rs237109	79471413	–	A/T
rs9343786	79471447	+	A/C
rs34396685	79471699	+	—/G
rs237108	79471734	+	C/T
rs28526821	79472111	+	A/G
rs9343787	79472325	+	A/C
rs9343788	79472577	+	A/G
rs237107	79472599	+	A/G
rs11337252	79472738	+	—/A
rs11322370	79472755	+	—/A
rs9448533	79473558	+	A/G
rs4706718	79473602	+	A/G
rs7773448	79474075	+	C/T
rs12662772	79474252	+	C/G
rs34988548	79474267	+	—/T
rs34521774	79474321	+	—/A
rs16890280	79474935	+	C/T
rs1180809	79474961	+	A/G
rs35874347	79475533	+	—/C
rs9341739	79475795	+	C/G
rs10485127	79476149	–	C/T
rs1782783	79476375	–	A/G
rs34305826	79476572	+	—/C
rs11758421	79477277	+	A/G
rs1180829	79477495	–	A/G
rs17642139	79477518	+	C/T
rs11380286	79477603	+	—/G
rs7748153	79477872	+	C/T
rs9341740	79479508	+	G/T
rs34794581	79480689	+	—/G
rs10613222	79480812	+	—/ ATATAT ATAT
rs10613221	79480824	+	—/AT
rs35653902	79480973	+	—/G
rs9352613	79481152	+	A/G
rs11363389	79481250	+	—/A
rs10589550	79481315	+	—/ ATATAT AT
rs34184424	79481323	+	—/ATAT
rs1180812	79481799	+	G/T

TABLE 6-continued

Polymorphic markers within the C06 region, between position 79,300,773 and 79,917,888 in NCBI Build 36. Shown is marker ID (rs-names), position in Build 36, strand and polymorphism type, where (—/N), N being any nucleotide or a plurality of nucleotides, corresponding to an insertion/deletion polymorphism (i.e. either the nucleotide(s) is present or not, as indicated).

Marker ID	Position Build 36	Strand	Polymorphism
rs1180813	79482210	+	C/T
rs1180814	79482234	+	A/G
rs10455352	79482310	+	A/G
rs1180815	79482567	+	C/T
rs1185719	79483043	+	A/G
rs1180816	79483108	+	A/C
rs9343789	79483300	+	A/G
rs9341741	79483557	+	A/G
rs35281441	79483695	+	A/C
rs1180817	79483705	+	A/G
rs6923778	79483808	+	A/G
rs1180818	79483938	+	C/G
rs35304238	79484265	+	—/A
rs28702778	79484289	+	A/C
rs28667093	79484464	+	A/G
rs12197635	79484466	+	A/G
rs11403769	79484690	+	—/A
rs33917829	79484698	+	—/A
rs35564110	79484699	+	—/A
rs1180819	79484743	+	A/G
rs1180820	79485455	+	A/G
rs1543481	79485804	+	C/G
rs1543482	79485857	+	A/G
rs1543483	79485890	+	A/T
rs1180821	79486391	+	A/G
rs9448534	79486474	+	C/T
rs28831831	79486721	+	C/T
rs2224461	79487062	+	A/G
rs2208518	79487184	+	G/T
rs13198615	79487271	+	A/G
rs3920564	79487560	+	G/T
rs6915548	79487586	+	A/G
rs1180822	79487770	+	A/G
rs35129774	79488647	+	—/G
rs1180823	79489645	+	A/G
rs13210865	79489811	+	A/G
rs7746175	79489924	+	A/T
rs11370388	79489978	+	—/A
rs35746612	79489979	+	—/A
rs35105486	79489988	+	—/A
rs1180824	79490242	+	A/G
rs1180825	79490569	+	G/T
rs1180826	79491321	+	C/G
rs1180827	79491347	+	C/G
rs28634504	79491970	+	A/G
rs1180828	79492141	+	C/G
rs3035346	79492475	+	—/G/GTG
rs35410463	79492476	+	—/GTG
rs34535315	79492501	+	—/G
rs35742744	79492502	+	—/T
rs1184721	79492711	+	C/T
rs1185343	79492909	+	C/G
rs34508299	79492924	+	—/T
rs2224462	79493658	+	C/G
rs12192834	79493674	+	C/T
rs7767460	79493730	+	G/T
rs6454073	79494060	+	A/G
rs7768079	79494100	+	G/T
rs7747874	79494113	+	C/T
rs7747911	79494214	+	A/T
rs35940523	79494339	+	—/A
rs9448536	79494391	+	C/G
rs9448537	79494467	+	A/G
rs10943570	79494466	+	A/G
rs5877627	79494624	+	—/CT
rs35909564	79494627	+	—/CT
rs3035349	79494638	+	—/CT/T
rs1570177	79494647	+	C/T
rs2321769	79494679	+	G/T
rs34358401	79494750	+	A/G

TABLE 6-continued

Polymorphic markers within the C06 region, between position 79,300,773 and 79,917,888 in NCBI Build 36. Shown is marker ID (rs-names), position in Build 36, strand and polymorphism type, where (—/N), N being any nucleotide or a plurality of nucleotides, corresponding to an insertion/deletion polymorphism (i.e. either the nucleotide(s) is present or not, as indicated).

Marker ID	Position Build 36	Strand	Polymorphism
rs7752898	79494868	+	C/T
rs9448538	79495167	+	G/T
rs2145685	79495471	+	A/G
rs9341742	79496948	+	C/T
rs9343792	79497004	+	C/T
rs9343793	79497122	+	C/T
rs12202166	79497374	+	A/G
rs6901911	79497718	+	A/G
rs35458046	79497892	+	—/C
rs7740607	79498009	+	C/T
rs9352615	79498212	+	C/G
rs9352616	79498222	+	C/T
rs9352617	79498373	+	A/C
rs9448540	79498394	+	G/T
rs7746203	79498898	+	A/G
rs9352618	79499147	+	C/T
rs9352619	79499433	+	A/G
rs11752556	79499668	+	C/T
rs7751066	79499807	+	A/C
rs9352620	79500266	+	G/T
rs11380936	79500730	+	—/A
rs6900332	79501060	+	C/T
rs9448542	79501084	+	A/C
rs35258079	79501132	+	—/C
rs9448543	79501153	+	A/T
rs12661502	79501197	+	C/T
rs9350769	79501280	+	A/G
rs9448544	79501600	+	C/T
rs9343794	79501644	+	A/G
rs7450313	79501839	+	C/T
rs4470810	79502002	+	G/T
rs1080857	79502085	+	C/T
rs4470811	79502097	+	C/T
rs2321770	79502127	+	C/T
rs7767636	79502775	+	A/G
rs7768125	79503108	+	A/G
rs9343796	79503266	+	C/T
rs9443612	79503406	+	C/T
rs12215204	79503784	+	A/G
rs9448545	79504354	+	C/T
rs9352621	79504806	+	A/C
rs9341743	79504981	+	A/G
rs9352622	79505238	+	A/T
rs9352623	79505367	+	A/C
rs7745733	79506026	+	C/T
rs9359341	79506207	+	C/T
rs7746057	79506232	+	A/C
rs4706063	79506593	+	A/G
rs4706721	79506594	+	A/G
rs4706064	79506627	+	C/T
rs4312941	79506920	+	A/G
rs7382759	79507470	+	A/C
rs6454075	79507724	+	A/G
rs4498306	79507894	+	C/T
rs36170402	79507898	+	—/G
rs4299783	79508072	+	C/T
rs7766318	79508234	+	A/C
rs12213140	79508449	+	A/G
rs4501390	79508621	+	G/T
rs4543321	79508705	+	C/T
rs4604236	79508754	+	A/C
rs36170201	79508906	+	—/C
rs9448546	79509562	+	C/T
rs6900430	79510134	+	A/G
rs9448548	79510151	+	A/G
rs35040883	79510284	+	—/C
rs6905141	79510644	+	A/G
rs7743640	79510794	+	A/G
rs7744731	79511190	+	C/G
rs9361425	79511397	+	C/T

TABLE 6-continued

Polymorphic markers within the C06 region, between position 79,300,773 and 79,917,888 in NCBI Build 36. Shown is marker ID (rs-names), position in Build 36, strand and polymorphism type, where (—/N), N being any nucleotide or a plurality of nucleotides, corresponding to an insertion/deletion polymorphism (i.e. either the nucleotide(s) is present or not, as indicated).

Marker ID	Position Build 36	Strand	Polymorphism
rs9352625	79511473	+	A/G
rs10428859	79511532	+	C/T
rs2180910	79511716	+	G/T
rs13199483	79511789	+	G/T
rs9352626	79511810	+	C/T
rs9343798	79512001	+	A/G
rs9352627	79512305	+	C/T
rs12528134	79512322	+	A/G
rs7382016	79512500	+	A/T
rs7382311	79512662	+	A/G
rs7383685	79512701	+	C/T
rs35420186	79512878	+	—/CAA
rs9448549	79512991	+	A/G
rs9350771	79513107	+	C/T
rs9350772	79513288	+	A/C
rs9350773	79513424	+	A/C
rs9359343	79513450	+	A/G
rs2145686	79513681	+	A/C
rs7759829	79513725	+	C/G
rs7759687	79513734	+	A/G
rs7760429	79513941	+	A/G
rs7760193	79514040	+	A/C
rs9352628	79514166	+	G/T
rs9361426	79514269	+	A/C
rs9448551	79514294	+	C/T
rs1998252	79514720	+	C/T
rs10943576	79514771	+	G/T
rs34981854	79514975	+	—/G
rs34769649	79515326	+	—/T
rs7766517	79515467	+	C/T
rs7766791	79515472	+	A/G
rs10559249	79515694	+	—/GTGT
rs5877628	79515693	+	—/TG
rs3035376	79515718	+	—/GT
rs1319575	79515770	+	C/T
rs3918524	79515816	+	A/G
rs1158575	79515925	+	C/T
rs4706066	79516496	+	C/T
rs2145687	79516920	+	C/T
rs2145688	79516936	+	C/T
rs34523548	79517003	+	—/T
rs35884007	79517112	+	—/G
rs35363076	79517166	+	—/G
rs961680	79517338	+	A/T
rs9359344	79517752	+	A/G
rs4141594	79517914	+	A/C
rs9443614	79517919	+	A/G
rs9350774	79518322	+	A/G
rs9294125	79518365	+	A/T
rs35542025	79518386	+	—/A
rs12528472	79518434	+	C/G
rs1475046	79518520	+	A/G
rs9294126	79518524	+	A/C
rs9352629	79518599	+	A/T
rs10943577	79518602	+	C/G
rs9343800	79518691	+	A/G
rs9352630	79518911	+	C/T
rs9352631	79518916	+	A/G
rs9352632	79518945	+	C/G
rs9343801	79518994	+	A/G
rs12196839	79519152	+	A/G
rs9352633	79519342	+	C/G
rs9352634	79519344	+	A/G
rs4706722	79519416	+	C/T
rs4706723	79519455	+	C/G
rs35622574	79519529	+	—/C
rs4706724	79519540	+	A/G
rs9448553	79520364	+	G/T
rs9350775	79520504	+	A/G
rs9350776	79520564	+	A/G

TABLE 6-continued

Polymorphic markers within the C06 region, between position 79,300,773 and 79,917,888 in NCBI Build 36. Shown is marker ID (rs-names), position in Build 36, strand and polymorphism type, where (—/N), N being any nucleotide or a plurality of nucleotides, corresponding to an insertion/deletion polymorphism (i.e. either the nucleotide(s) is present or not, as indicated).

Marker ID	Position Build 36	Strand	Polymorphism
rs4590227	79520629	+	A/G
rs7451373	79520890	+	C/T
rs9350777	79520900	+	A/C
rs9361427	79521580	+	A/T
rs2321771	79522159	+	C/T
rs6454077	79522624	+	A/G
rs4706725	79523110	+	A/G
rs4706726	79523256	+	C/G
rs4706727	79523430	+	C/T
rs4706728	79523530	+	G/T
rs4706729	79524311	+	G/T
rs4706730	79524622	+	A/G
rs35493328	79524755	+	—/A
rs9343804	79524771	+	A/G
rs9343805	79524845	+	G/T
rs4706731	79525017	+	C/T
rs6916201	79525202	+	C/T
rs4706732	79525233	+	A/C
rs4706733	79525331	+	C/T
rs4706734	79525369	+	C/T
rs4706067	79525544	+	A/G
rs4706735	79525556	+	C/T
rs4706068	79525824	+	C/T
rs7758474	79525893	+	C/G
rs7758382	79526025	+	C/T
rs7758411	79526113	+	A/G
rs7758668	79526149	+	C/G
rs7758709	79526220	+	A/C
rs9343809	79526430	+	A/G
rs9352638	79526528	+	A/G
rs9352639	79526557	+	A/G
rs9352640	79526632	+	C/T
rs9359345	79526635	+	A/C
rs9361430	79526795	+	C/T
rs9361431	79526796	+	A/G
rs12215488	79526895	+	A/G
rs4277969	79527116	+	C/T
rs9343810	79527190	+	C/G
rs9343811	79527285	+	C/T
rs36159791	79527300	+	—/G
rs6939408	79527324	+	A/G
rs9361432	79527332	+	A/G
rs9352641	79527639	+	A/G
rs9361433	79527970	+	A/G
rs9352642	79528071	+	A/C
rs4706069	79528287	+	C/T
rs11751339	79528440	+	A/C
rs4706070	79528478	+	A/G
rs36193003	79528479	+	AA/GG
rs4706071	79528479	+	A/G
rs9359346	79528869	+	A/G
rs7746103	79529063	+	C/T
rs9352645	79529280	+	C/G
rs7746449	79529347	+	A/C
rs9352646	79529377	+	A/G
rs4419638	79529395	+	C/G
rs36146147	79529439	+	—/G
rs9341748	79529663	+	A/G
rs9343814	79529792	+	C/G
rs9448558	79529987	+	C/G
rs10943581	79530174	+	C/T
rs28716526	79530437	+	A/G
rs11752708	79530459	+	G/T
rs11752686	79530498	+	C/T
rs6899455	79530697	+	C/T
rs34374962	79530898	+	A/C
rs9448559	79531201	+	A/G
rs6920807	79531450	+	A/T
rs2135769	79532044	+	A/G
rs4706736	79532195	+	A/T

TABLE 6-continued

Polymorphic markers within the C06 region, between position 79,300,773 and 79,917,888 in NCBI Build 36. Shown is marker ID (rs-names), position in Build 36, strand and polymorphism type, where (—/N), N being any nucleotide or a plurality of nucleotides, corresponding to an insertion/deletion polymorphism (i.e. either the nucleotide(s) is present or not, as indicated).

Marker ID	Position Build 36	Strand	Polymorphism
rs4706072	79532210	+	A/G
rs1588086	79532606	+	C/T
rs1588087	79532636	+	A/T
rs2321772	79532909	+	G/T
rs9443616	79532925	+	A/G
rs2321773	79532962	+	A/G
rs2321774	79533169	+	C/T
rs9443617	79533254	+	A/G
rs34749198	79533559	+	—/T
rs1073211	79533575	–	C/T
rs28845538	79533674	+	C/T
rs2135770	79533747	+	A/C
rs9341750	79534203	+	C/T
rs6938951	79534339	+	A/C
rs6939263	79534367	+	C/T
rs9359348	79534401	+	A/T
rs6900794	79534563	+	C/T
rs34763883	79534693	+	—/A
rs6901015	79534742	+	C/T
rs6924048	79534918	+	C/T
rs36084053	79535093	+	—/C
rs10943583	79535183	+	C/G
rs35165607	79535238	+	—/C
rs34534036	79535250	+	—/C
rs11755934	79535340	+	C/T
rs2321775	79535509	+	C/T
rs9359350	79535870	+	C/G
rs9361437	79536054	+	C/T
rs9361438	79536280	+	C/T
rs9352648	79536460	+	A/G
rs9341751	79536555	+	C/T
rs9448560	79536601	+	A/G
rs9448561	79536715	+	A/G
rs9343820	79537177	+	A/T
rs11965322	79537414	+	A/T
rs36082173	79537823	+	—/T
rs6923812	79538338	+	C/T
rs9350781	79538534	+	A/T
rs1876389	79538651	+	A/T
rs35000167	79538888	+	—/T
rs11961822	79539174	+	A/G
rs35722542	79539754	+	—/A
rs12663824	79539849	+	A/C
rs1021987	79539884	+	C/G
rs1507151	79539965	+	C/T
rs1507152	79540193	+	C/T
rs1567169	79540652	+	C/T
rs1507153	79541105	+	A/C
rs35498910	79541112	+	—/T
rs9448562	79541799	+	G/T
rs1876390	79542282	+	C/T
rs9448563	79543216	+	A/G
rs9448564	79543231	+	C/T
rs9448565	79543237	+	C/T
rs16890304	79543377	+	A/G
rs1876391	79543470	+	C/T
rs6454082	79544001	+	C/T
rs4555886	79544101	+	A/T
rs34032635	79544308	+	—/T
rs34806029	79544385	+	—/G
rs11758151	79544940	+	C/T
rs11758164	79544958	+	G/T
rs6928279	79545677	+	C/T
rs9361440	79546395	+	A/C
rs9352649	79546502	+	G/T
rs34850892	79547499	+	—/C
rs9361441	79547685	+	A/G
rs35665788	79547866	+	—/T
rs35275890	79549004	+	—/A
rs35562053	79549016	+	A/T

TABLE 6-continued

Polymorphic markers within the C06 region, between position 79,300,773 and 79,917,888 in NCBI Build 36. Shown is marker ID (rs-names), position in Build 36, strand and polymorphism type, where (—/N), N being any nucleotide or a plurality of nucleotides, corresponding to an insertion/deletion polymorphism (i.e. either the nucleotide(s) is present or not, as indicated).

Marker ID	Position Build 36	Strand	Polymorphism
rs6935486	79549211	+	A/G
rs9359351	79549252	+	A/G
rs11755568	79550337	+	C/T
rs34268443	79550347	+	—/C
rs6942344	79550522	+	C/T
rs2321893	79550527	+	C/T
rs9352650	79550613	+	A/G
rs11751437	79550636	+	A/G
rs9361442	79550764	+	A/G
rs6904016	79550772	+	C/T
rs4055608	79550977	+	C/T
rs9350782	79551187	+	A/G
rs9352652	79551451	+	A/G
rs10806148	79551623	+	A/G
rs34335705	79552378	+	C/T
rs12181706	79552458	+	C/G
rs9361443	79552769	+	A/C
rs2874642	79552903	+	A/G
rs12176501	79553029	+	C/T
rs9343822	79553040	+	A/T
rs7773850	79553042	+	A/T
rs7773851	79553044	+	A/T
rs11757519	79553160	+	C/T
rs35940795	79553244	+	—/C
rs35004706	79553408	+	—/C
rs9352653	79553582	+	A/G
rs9343823	79553825	+	A/C
rs9343824	79554288	+	A/G
rs35245361	79554378	+	—/A/T
rs1507155	79554584	+	A/G
rs2021541	79554588	+	A/G
rs13210672	79554590	+	A/G
rs9343826	79554632	+	A/G
rs1507156	79554776	+	A/G
rs34136836	79555385	+	—/G
rs34958301	79556015	+	—/G
rs9361444	79556792	+	C/T
rs1507149	79556805	–	C/G
rs9352654	79557000	+	A/G
rs9343827	79557755	+	A/G
rs9359352	79558729	+	C/T
rs7757382	79558996	+	C/G
rs10943585	79559128	+	C/G
rs9361445	79559275	+	C/T
rs5877629	79559295	+	—/T
rs1827992	79559524	–	A/G
rs7762022	79559578	+	A/C
rs6926463	79559890	+	A/G
rs6454083	79560137	+	C/T
rs9352655	79560142	+	A/T
rs1507154	79560419	+	C/T
rs1476304	79560439	+	C/T
rs1476305	79560605	+	G/T
rs4628052	79560919	+	A/G
rs13200035	79561004	+	C/T
rs13214259	79561046	+	A/C
rs13200136	79561064	+	C/T
rs13214670	79561072	+	A/G
rs13214372	79561084	+	A/G
rs13200153	79561107	+	C/T
rs13214383	79561121	+	A/G
rs28781665	79561419	+	A/G
rs1848194	79562087	+	C/T
rs35374025	79562246	+	—/T
rs1911513	79562355	+	A/G
rs9448568	79562434	+	A/G
rs7774691	79562517	+	C/G
rs9352657	79562804	+	C/G
rs7741245	79563215	+	A/G
rs7741407	79563307	+	A/G

TABLE 6-continued

Polymorphic markers within the C06 region, between position 79,300,773 and 79,917,888 in NCBI Build 36. Shown is marker ID (rs-names), position in Build 36, strand and polymorphism type, where (—/N), N being any nucleotide or a plurality of nucleotides, corresponding to an insertion/deletion polymorphism (i.e. either the nucleotide(s) is present or not, as indicated).

Marker ID	Position Build 36	Strand	Polymorphism
rs7761613	79563435	+	C/T
rs35613790	79563516	+	—/A
rs6454084	79563604	+	A/G
rs4446522	79564225	+	A/T
rs6931419	79564240	+	A/T
rs4334937	79564258	+	C/T
rs12527806	79564386	+	A/T
rs3967330	79564533	+	A/C
rs9448572	79565438	+	G/T
rs10943587	79565451	+	C/T
rs9443619	79565631	+	C/T
rs7756996	79566086	+	A/C
rs11753266	79566107	+	C/T
rs1857957	79566184	–	C/G
rs28759673	79566270	+	G/T
rs2321896	79566463	+	C/G
rs41503746	79566463	–	C/G
rs35414898	79566540	+	—/A
rs34037147	79566911	+	—/C
rs10943588	79567713	+	A/C
rs11751036	79567797	+	C/T
rs2202662	79568057	–	G/T
rs2202661	79568299	–	A/G
rs2202660	79568463	–	G/T
rs9448573	79569097	+	C/T
rs6913028	79570309	+	C/T
rs6454085	79570611	+	C/G
rs4706737	79570764	+	A/G
rs35196425	79570832	+	—/T
rs4706075	79570837	+	C/G
rs4706076	79570871	+	C/CA/T/TG
rs4706738	79570872	+	A/G
rs2202659	79571328	–	A/G
rs12662944	79571375	+	A/T
rs9350784	79572125	+	C/T
rs9350785	79572304	+	C/T
rs9448574	79573020	+	A/C
rs9448575	79573525	+	G/T
rs1814219	79573704	–	G/T
rs13216900	79573706	+	A/G
rs34791687	79573717	+	—/G
rs9350786	79574025	+	G/T
rs35713298	79574030	+	—/GGG
rs13217367	79574256	+	A/T
rs9343834	79574390	+	A/G
rs12203336	79575034	+	G/T
rs35790661	79575375	+	—/CA
rs2202658	79576388	–	C/T
rs906320	79576561	–	A/G
rs41269335	79576661	+	G/T
rs34943334	79576824	+	A/G
rs906319	79577408	–	C/T
rs41269337	79577988	+	A/G
rs6454086	79578882	+	C/T
rs9361448	79579645	+	G/T
rs9352659	79580583	+	A/G
rs9448576	79580987	+	C/G
rs2202663	79581585	+	C/T
rs1395655	79581612	+	C/T
rs7773491	79582941	+	C/T
rs4640849	79583469	+	A/G
rs35044999	79584659	+	—/C
rs12524858	79586232	+	G/T
rs2202664	79586366	+	C/G
rs9448577	79586917	+	C/G
rs28814638	79587149	+	A/G
rs34428579	79587468	+	—/A
rs12209635	79588934	+	C/T
rs955765	79589329	–	A/G
rs5877630	79589377	+	—/G

TABLE 6-continued

Polymorphic markers within the C06 region, between position 79,300,773 and 79,917,888 in NCBI Build 36. Shown is marker ID (rs-names), position in Build 36, strand and polymorphism type, where (—/N), N being any nucleotide or a plurality of nucleotides, corresponding to an insertion/deletion polymorphism (i.e. either the nucleotide(s) is present or not, as indicated).

Marker ID	Position Build 36	Strand	Polymorphism
rs9448578	79589928	+	G/T
rs4706739	79590001	+	C/T
rs12213359	79590746	+	A/C
rs10556588	79592115	+	—/AGAA
rs12195716	79592131	+	C/T
rs6902294	79593001	+	G/T
rs1567168	79593174	+	A/C
rs2174740	79593284	+	A/G
rs2135767	79593386	+	C/T
rs6454088	79594398	+	C/T
rs12194457	79595224	+	A/G
rs35356883	79595302	+	—/G
rs12194642	79595510	+	A/G
rs9343838	79595869	+	A/G
rs10639111	79596351	+	—/GAGA
rs34962848	79596352	+	—/GAGA
rs34665735	79596358	+	—/AGAG
rs35366557	79596414	+	—/G
rs16890324	79596828	+	A/G
rs13217987	79597357	+	A/G
rs1963638	79597835	+	G/T
rs2013420	79597934	+	A/G
rs16890325	79597947	+	C/T
rs9352662	79598210	+	A/G
rs28626679	79598705	+	C/G
rs35393092	79598862	+	—/T
rs16890326	79599251	+	C/T
rs34305313	79600125	+	—/A
rs33920803	79600126	+	—/A
rs12110531	79600198	+	C/G
rs6912683	79600211	+	A/C
rs16890328	79600713	+	A/C
rs7754715	79600777	+	A/G
rs34253750	79601120	+	—/G
rs13208855	79602240	+	G/T
rs16890330	79602923	+	A/C
rs1021986	79603853	+	C/G
rs35242601	79604056	+	—/T
rs13220688	79604565	+	C/T
rs16890331	79605080	+	C/T
rs1507150	79605316	+	A/T
rs4706077	79605564	+	A/G
rs10806150	79605891	+	A/G
rs12664947	79606191	+	A/T
rs1542977	79607026	+	G/T
rs35949145	79607341	+	—/A
rs2174741	79607599	+	A/C
rs34567509	79608189	+	—/C
rs9448579	79608431	+	C/T
rs9448580	79608531	+	C/G
rs1027813	79608837	–	A/C
rs35909912	79609084	+	C/T
rs34385822	79609087	+	C/T
rs35544399	79609089	+	C/T
rs34033174	79609112	+	C/T
rs5877631	79609384	+	—/T
rs35937908	79609385	+	—/T
rs34696113	79609390	+	—/T
rs33954612	79609391	+	—/T
rs12664403	79610047	+	G/T
rs2135766	79610075	–	A/G
rs9448581	79610097	+	A/G
rs35179848	79610136	+	A/C
rs11332279	79610357	+	—/A
rs1567167	79610546	–	A/G
rs4415132	79610826	+	C/T
rs6926537	79610912	+	A/T
rs17741785	79610991	+	A/G
rs1507148	79611110	–	C/T
rs4409146	79611326	+	C/T

TABLE 6-continued

Polymorphic markers within the C06 region, between position 79,300,773 and 79,917,888 in NCBI Build 36. Shown is marker ID (rs-names), position in Build 36, strand and polymorphism type, where (—/N), N being any nucleotide or a plurality of nucleotides, corresponding to an insertion/deletion polymorphism (i.e. either the nucleotide(s) is present or not, as indicated).

Marker ID	Position Build 36	Strand	Polymorphism
rs34490997	79611333	+	—/G
rs9361451	79611774	+	C/T
rs16890334	79612885	+	C/T
rs12196485	79613590	+	A/G
rs4147183	79613765	+	C/G
rs36024489	79614221	+	G/T
rs9352663	79614883	+	C/T
rs35934464	79615331	+	—/C
rs971994	79616321	–	C/G
rs7454053	79616439	+	A/G
rs10223389	79616629	+	A/G
rs12214796	79617787	+	C/T
rs17798356	79618153	+	A/G
rs12190108	79619374	+	C/T
rs4421161	79620938	+	A/G
rs12213652	79621099	+	A/G
rs2321894	79621148	+	A/G
rs9448583	79621405	+	A/G
rs9361454	79621963	+	—/G/T
rs12176511	79622440	+	A/G
rs34132605	79622874	+	—/G
rs9352664	79622881	+	G/T
rs10455354	79622949	+	A/G
rs2874643	79623036	+	A/G
rs1960542	79623362	+	C/T
rs9352665	79624438	+	C/G
rs9361455	79624601	+	A/G
rs34916187	79624764	+	—/G
rs12661039	79625256	+	C/T
rs4682456	79625580	–	C/T
rs7449459	79625728	+	C/T
rs6936109	79626595	+	A/G
rs12201183	79626839	+	A/G
rs6937465	79627064	+	G/T
rs9361458	79627515	+	C/T
rs11381253	79627547	+	—/A
rs34502239	79627557	+	—/A
rs9765849	79627608	+	A/G
rs9352666	79628903	+	C/G
rs9352667	79629015	+	C/T
rs9352668	79629397	+	A/G
rs9448584	79629518	+	G/T
rs9448585	79629560	+	A/G
rs9361459	79629641	+	A/G
rs9343841	79630723	+	C/G
rs6923327	79631594	+	A/G
rs10943595	79632010	+	C/G
rs34199187	79632011	+	CC/GT
rs10943596	79632011	+	C/T
rs34658311	79632386	+	A/T
rs11444087	79632386	+	—/T
rs7760883	79632388	+	—/A/T
rs35635397	79632389	+	—/A
rs16890347	79632927	+	C/T
rs9443621	79633218	+	A/G
rs41269339	79634131	+	C/G
rs9350789	79634363	+	A/C
rs9341753	79634515	+	C/T
rs12153837	79635921	+	A/C
rs12527589	79636178	+	C/T
rs10455355	79636221	+	C/T
rs34431699	79637008	+	—/C
rs6941317	79637771	+	A/C
rs7738062	79638242	+	C/G
rs4706740	79639381	+	A/C
rs34204884	79639456	+	C/T
rs9443622	79639509	+	C/T
rs4706078	79639525	+	C/T
rs35373380	79639573	+	C/T
rs12193104	79639633	+	A/G

TABLE 6-continued

Polymorphic markers within the C06 region, between position 79,300,773 and 79,917,888 in NCBI Build 36. Shown is marker ID (rs-names), position in Build 36, strand and polymorphism type, where (—/N), N being any nucleotide or a plurality of nucleotides, corresponding to an insertion/deletion polymorphism (i.e. either the nucleotide(s) is present or not, as indicated).

Marker ID	Position Build 36	Strand	Polymorphism
rs12660767	79639652	+	C/T
rs35962544	79639717	+	—/AA
rs12193319	79640156	+	A/C
rs6454089	79640821	+	C/T
rs9352669	79640860	+	G/T
rs9352670	79641152	+	A/G
rs9341754	79641692	+	A/C
rs34538995	79641946	+	—/GAAA
rs9448586	79642219	+	A/G
rs34409101	79642323	+	—/T
rs9343843	79642344	+	C/T
rs35304712	79643086	+	C/T
rs9343844	79643182	+	A/T
rs9350792	79643892	+	A/G
rs35439908	79645611	+	—/G
rs9448587	79645751	+	A/G
rs9341755	79645767	+	C/G
rs9361460	79646186	+	C/G
rs9448588	79646780	+	G/T
rs9359354	79647104	+	A/G
rs35560175	79647373	+	—/A
rs34453824	79647874	+	—/C
rs2174743	79648524	–	C/T
rs2135772	79648767	–	A/C
rs1021988	79649380	–	A/G
rs35897423	79650428	+	—/C
rs9352671	79651798	+	A/C
rs6908105	79651816	+	A/G
rs4055605	79651890	+	—/TCTTA
rs35817888	79651891	+	—/TCTTA
rs35754813	79652867	+	—/A
rs2321895	79654080	+	C/T
rs35355117	79654223	+	—/C
rs9352672	79654253	+	C/T
rs34228023	79654468	+	—/A
rs35503114	79654971	+	—/T
rs34717008	79655526	+	C/T
rs36108843	79655546	+	—/C
rs34900932	79655547	+	—/T
rs34933654	79655550	+	C/T
rs34963207	79656023	+	—/A
rs9361462	79656183	+	A/G
rs35606311	79656863	+	—/A
rs12192086	79657229	+	A/G
rs9448589	79657767	+	G/T
rs9352673	79659462	+	G/T
rs9359355	79659533	+	A/G
rs9343845	79659752	+	A/G
rs36114710	79659754	+	A/G
rs9352674	79660060	+	G/T
rs35774009	79662784	+	—/A
rs36087293	79663083	+	—/G
rs9448590	79663148	+	C/G
rs9448591	79663209	+	C/T
rs36004777	79663275	+	—/A
rs4327648	79663334	+	C/T
rs10525714	79664847	+	—/ ATATAT
rs35395481	79664848	+	—/ ATATAT
rs34482864	79664856	+	—/AT
rs10700674	79664871	+	—/AT
rs7776322	79666464	+	A/T
rs2174742	79666820	+	G/T

TABLE 6-continued

Polymorphic markers within the C06 region, between position 79,300,773 and 79,917,888 in NCBI Build 36. Shown is marker ID (rs-names), position in Build 36, strand and polymorphism type, where (—/N), N being any nucleotide or a plurality of nucleotides, corresponding to an insertion/deletion polymorphism (i.e. either the nucleotide(s) is present or not, as indicated).

Marker ID	Position Build 36	Strand	Polymorphism
rs2135771	79667075	+	C/T
rs6941107	79667642	+	A/G
rs10943600	79668224	+	A/G
rs9343846	79668848	+	A/T
rs35533616	79669465	+	—/A
rs9352675	79669519	+	A/G
rs1354831	79670295	+	C/T
rs1354832	79670482	+	C/T
rs35112046	79671111	+	—/C
rs9443623	79671372	+	C/T
rs4706079	79671927	+	A/G
rs4706742	79672269	+	C/T
rs4706743	79672512	+	G/T
rs2174744	79673008	+	A/T
rs9448592	79673037	+	C/G
rs35935416	79673657	+	—/T
rs6915030	79674241	+	C/T
rs9361466	79675071	+	C/T
rs10806151	79676098	+	C/T
rs11402304	79676284	+	—/T
rs7756858	79676687	+	A/G
rs9443624	79676995	+	A/G
rs6921318	79677095	+	A/G
rs7758407	79677426	+	C/G
rs34373655	79677787	+	—/T
rs9361467	79677817	+	A/G
rs9343848	79677820	+	C/T
rs9361468	79677933	+	A/G
rs9448594	79679933	+	A/T
rs9448595	79680349	+	A/G
rs1963080	79681257	+	A/G
rs5877633	79681440	+	—/G
rs35590303	79682202	+	—/C
rs2063124	79683041	+	C/T
rs7756648	79683805	+	A/T
rs35313944	79684092	+	—/A
rs9343849	79684179	+	A/G
rs12196457	79684462	+	A/T
rs7767182	79685667	+	A/C
rs35777909	79685724	+	—/G
rs36012949	79685747	+	—/C
rs9448596	79686148	+	C/T
rs9443626	79686283	+	C/G
rs9352676	79686718	+	A/G
rs7750836	79688302	+	C/G
rs9350794	79688561	+	C/T
rs7755754	79689008	+	A/G
rs36181347	79689691	+	—/A
rs7760866	79689848	+	C/G
rs9361472	79690160	+	G/T
rs36132801	79690225	+	—/G
rs9448597	79690306	+	C/T
rs9689724	79690631	+	A/G
rs9343851	79690827	+	C/G
rs34433262	79690888	+	—/C
rs9688928	79691098	+	A/C
rs28826982	79691188	+	A/G
rs34236947	79691189	+	AC/GG
rs28811946	79691189	+	C/G
rs9359358	79692407	+	C/T
rs2089416	79692807	+	G/T
rs34521933	79693343	+	—/C
rs2135768	79693482	+	C/T
rs7744604	79694234	+	A/C
rs10755377	79694644	+	C/T
rs5877634	79696377	+	—/T
rs11430514	79697407	+	—/T
rs35387172	79697408	+	—/T
rs9350795	79697410	+	A/T
rs12665761	79697747	+	C/T

TABLE 6-continued

Polymorphic markers within the C06 region, between position 79,300,773 and 79,917,888 in NCBI Build 36. Shown is marker ID (rs-names), position in Build 36, strand and polymorphism type, where (—/N), N being any nucleotide or a plurality of nucleotides, corresponding to an insertion/deletion polymorphism (i.e. either the nucleotide(s) is present or not, as indicated).

Marker ID	Position Build 36	Strand	Polymorphism
rs13205569	79697785	+	G/T
rs2321897	79698887	+	C/T
rs1911512	79699043	+	C/T
rs9343853	79699300	+	C/T
rs12660760	79699828	+	C/T
rs12660770	79699923	+	C/T
rs35416532	79700122	+	—/TTT
rs9343854	79700770	+	A/C
rs1044313	79702339	–	A/T
rs35580162	79703022	+	—/C
rs35881759	79703274	+	—/C
rs35125759	79703290	+	—/C
rs1044309	79703294	–	C/T
rs34261531	79703338	+	—/C
rs5877635	79704127	+	—/T
rs35000895	79704129	+	—/T
rs4464748	79704697	+	C/G
rs10654924	79706512	+	—/AA
rs34701016	79706513	+	—/AA
rs13191571	79706985	+	G/T
rs36155238	79706984	+	—/T
rs36160851	79706985	+	—/T
rs36170973	79706986	+	—/T
rs36132527	79707051	+	—/G
rs11547229	79707066	+	A/G
rs6900790	79707081	+	C/T
rs34609668	79707212	+	G/T
rs2485701	79707264	+	A/G
rs1876387	79707310	+	A/G
rs1876388	79707370	+	G/T
rs34463462	79707429	+	G/T
rs10574664	79707958	+	—/AC
rs28606484	79709319	+	C/T
rs9350796	79710116	+	C/T
rs6454090	79710425	+	—/ A/AA/AA A/T/TT
rs6454091	79710426	+	A/T
rs35306286	79710425	+	—/AAA
rs11370303	79710434	+	—/A
rs11432700	79710436	+	—/A
rs11447037	79710449	+	—/A
rs9443629	79710479	+	A/C
rs34717491	79710843	+	—/C
rs7740307	79710873	+	A/T
rs9688399	79711374	+	A/G
rs5877636	79711409	+	—/A
rs33977407	79711410	+	—/A
rs10943605	79712196	+	A/G
rs1135076	79712453	–	A/G
rs1056960	79712497	–	C/T
rs34050775	79713035	+	—/A
rs36048894	79713183	–	A/C
rs1056959	79713195	–	A/G
rs1056958	79713223	–	C/T
rs2275291	79713281	–	A/T
rs2275290	79713289	–	C/T
rs9361473	79713761	+	C/T
rs1984195	79714110	–	C/T
rs11370597	79714395	+	—/C
rs1283320	79714834	+	C/G
rs35766012	79714947	+	—/T
rs35205946	79715066	+	—/G
rs4706745	79715247	+	C/T
rs2063123	79715254	+	C/T
rs12529691	79715751	+	A/G
rs2174739	79715889	+	A/G
rs9343855	79716132	+	G/T
rs34526870	79716648	+	—/C
rs35018864	79717062	+	—/C

TABLE 6-continued

Polymorphic markers within the C06 region, between position 79,300,773 and 79,917,888 in NCBI Build 36. Shown is marker ID (rs-names), position in Build 36, strand and polymorphism type, where (—/N), N being any nucleotide or a plurality of nucleotides, corresponding to an insertion/deletion polymorphism (i.e. either the nucleotide(s) is present or not, as indicated).

Marker ID	Position Build 36	Strand	Polymorphism
rs2050661	79717844	–	A/G
rs28623652	79718361	+	C/T
rs9443630	79718517	+	G/T
rs10943606	79718496	+	G/T
rs9448600	79719788	+	A/C
rs9443631	79720837	+	C/T
rs9443632	79721159	+	C/T
rs10455356	79721467	+	C/T
rs7753358	79721929	+	A/T
rs11316583	79723594	+	—/T
rs5877637	79724015	+	—/A
rs35159735	79724505	+	—/C
rs34936739	79725919	+	—/C
rs35865427	79726072	+	—/C
rs12665739	79727563	+	C/T
rs6940635	79727692	+	C/T
rs946022	79728852	+	G/T
rs3805746	79729157	+	C/T
rs3805747	79729241	+	A/G
rs34841569	79729665	–	A/C
rs4706746	79730895	+	A/G
rs13202531	79730981	+	C/T
rs35504170	79731083	+	—/C
rs10943608	79731648	+	C/T
rs3834844	79731991	+	—/CTT
rs3763160	79731994	+	A/G
rs9350797	79732420	+	A/G
rs11964204	79732781	+	A/G
rs10943609	79733047	+	A/T
rs1572586	79733060	+	C/T
rs1538234	79733298	+	C/T
rs3834845	79733766	+	—/C
rs34920411	79734822	+	—/C
rs9343856	79734930	+	A/G
rs10531246	79735174	+	—/TAAT
rs34584316	79736188	+	—/T
rs12663267	79736218	+	C/G
rs7742746	79736246	+	G/T
rs7742874	79736287	+	A/G
rs7742431	79736296	+	A/G
rs34480532	79736437	+	—/A
rs7768255	79736633	+	A/G
rs7768001	79736672	+	A/C
rs7768414	79736727	+	C/G
rs9443633	79736782	+	C/T
rs9448601	79738088	+	C/T
rs9448602	79738107	+	A/G
rs4406190	79738370	+	A/G
rs10806154	79739086	+	C/T
rs12190940	79739190	+	A/G
rs7741943	79739286	+	A/G
rs9448603	79739333	+	A/G
rs36146106	79739418	+	—/A
rs9352679	79739848	+	A/G
rs9341756	79739909	+	C/T
rs9350798	79739980	+	A/C
rs9341757	79739993	+	G/T
rs7766920	79740022	+	C/T
rs7746653	79740031	+	C/G
rs7751287	79740610	+	A/G
rs36166556	79740631	+	—/T
rs36128361	79741059	+	C/G
rs10943610	79741136	+	A/G
rs9352681	79741292	+	A/G
rs9343857	79741450	+	C/G
rs9343858	79741488	+	C/T
rs12182951	79742891	+	A/G
rs12182952	79742924	+	A/C
rs9448604	79743377	+	A/G
rs9448605	79743416	+	G/T

TABLE 6-continued

Polymorphic markers within the C06 region, between position 79,300,773 and 79,917,888 in NCBI Build 36. Shown is marker ID (rs-names), position in Build 36, strand and polymorphism type, where (—/N), N being any nucleotide or a plurality of nucleotides, corresponding to an insertion/deletion polymorphism (i.e. either the nucleotide(s) is present or not, as indicated).

Marker ID	Position Build 36	Strand	Polymorphism
rs36149780	79743416	+	G/T
rs4594915	79743583	+	A/C
rs11282710	79744026	+	—/ TTCAAG CACC
rs36124591	79744030	+	—/ AAGCAC CTTC
rs34344828	79744037	+	—/ TTCAAG CAC
rs7750810	79744283	+	A/T
rs12209235	79745085	+	C/T
rs34362578	79745461	+	—/G
rs4624830	79745780	+	A/T
rs1538235	79746169	+	C/T
rs1572584	79747009	+	A/G
rs34246619	79747058	+	—/A
rs1572585	79747295	+	C/T
rs10943611	79747894	+	A/G
rs9343859	79749118	+	A/C
rs11547228	79749470	–	C/T
rs10642979	79750856	+	—/GT
rs35922935	79750857	+	—/GT
rs35769552	79751527	+	—/G
rs1890229	79751748	+	C/T
rs1890230	79752043	+	A/G
rs9352682	79752074	+	C/T
rs35730468	79753387	+	—/AAT
rs4623209	79753656	+	G/T
rs35399714	79753801	+	—/T
rs12529043	79754574	+	A/G
rs10943612	79755099	+	C/T
rs35529955	79755508	+	—/T
rs4144107	79755536	+	—/A/C
rs34495466	79755537	+	—/A
rs3902856	79756556	+	C/T
rs1415862	79756757	+	A/G
rs1415863	79756878	+	A/G
rs3818839	79757044	+	C/G
rs34665480	79757153	+	A/C
rs35828088	79757480	+	—/A
rs9359359	79757699	+	C/T
rs3841156	79757786	–	—/AGA
rs3841155	79757996	–	—/TCT
rs7749615	79758494	+	G/T
rs6454092	79758691	+	A/G
rs12208915	79759454	+	A/G
rs9359360	79759515	+	C/T
rs9359361	79762302	+	C/G
rs35279139	79762390	+	—/T
rs6940637	79762564	+	C/T
rs6904138	79763733	+	A/G
rs35057263	79763873	–	C/T
rs41269341	79764094	+	C/T
rs11752126	79764642	+	C/T
rs7747479	79764719	+	A/C
rs36000864	79767181	+	A/G
rs9443636	79767375	+	C/T
rs9361477	79767525	+	C/T
rs13218407	79767680	+	A/C
rs13218727	79767681	+	A/G
rs9361478	79768691	+	A/G
rs34042644	79769661	+	G/T
rs2065986	79769884	+	C/T
rs9443637	79771427	+	C/T
rs13191068	79771586	+	C/T
rs11965967	79771803	+	C/T
rs9448607	79772339	+	A/G
rs6907674	79773483	+	A/T

TABLE 6-continued

Polymorphic markers within the C06 region, between position 79,300,773 and 79,917,888 in NCBI Build 36. Shown is marker ID (rs-names), position in Build 36, strand and polymorphism type, where (—/N), N being any nucleotide or a plurality of nucleotides, corresponding to an insertion/deletion polymorphism (i.e. either the nucleotide(s) is present or not, as indicated).

Marker ID	Position Build 36	Strand	Polymorphism
rs35415106	79774112	+	—/TTT
rs9352683	79775514	+	G/T
rs34509958	79776185	+	—/G
rs9443638	79777586	+	A/T
rs9448608	79777881	+	C/T
rs1933238	79778128	+	A/C
rs11754374	79778672	+	G/T
rs7766491	79778959	+	C/T
rs4706747	79779358	+	A/G
rs4706748	79779391	+	A/G
rs4637600	79780227	+	A/T
rs9350799	79780370	+	A/C
rs9361479	79780474	+	A/T
rs35887627	79780475	+	AC/TT
rs9359362	79780475	+	C/T
rs9361480	79781148	+	A/G
rs34015061	79781739	+	—/T
rs9361481	79783469	+	A/T
rs36092348	79784000	–	A/G
rs1338023	79785047	+	G/T
rs9350800	79786208	+	A/C
rs11754419	79786367	+	A/G
rs9718121	79786606	+	A/T
rs35727754	79786754	+	—/A
rs1832396	79787561	–	C/G
rs34244224	79787746	+	A/C
rs34815601	79788716	+	—/A
rs11315927	79789321	+	—/T
rs9352685	79790968	+	C/T
rs2050659	79791088	+	A/C
rs2050660	79791445	+	C/T
rs35999901	79791481	+	—/G
rs28449859	79791564	+	C/T
rs34111968	79791750	+	—/A
rs9443639	79791873	+	C/T
rs7775074	79792805	+	C/G
rs34655287	79792904	+	—/A
rs11326550	79792916	+	—/A
rs7742034	79793825	+	A/G
rs28532298	79795101	+	C/T
rs35744497	79795678	+	C/T
rs9448609	79795708	+	A/G
rs3929865	79795727	+	C/T
rs9343860	79795729	+	A/G
rs3929866	79795824	+	A/G
rs13218541	79795927	+	C/T
rs3929867	79796069	+	A/G
rs9448610	79796341	+	A/G
rs6918296	79797639	+	C/T
rs4565265	79798677	+	A/G
rs2095724	79798820	+	C/T
rs7741282	79799097	+	A/G
rs35793703	79799130	+	—/G
rs2105143	79799666	+	A/G
rs1538233	79800454	+	G/T
rs7751422	79800799	+	C/T
rs35760468	79800851	+	—/G
rs9343861	79801587	+	A/C
rs10943613	79801826	+	C/T
rs11963444	79802291	+	C/G
rs34875528	79803382	+	—/A
rs9359363	79803610	+	C/T
rs9448612	79803872	+	A/G
rs12180022	79803813	+	A/G
rs9448613	79803942	+	A/G
rs9448614	79804316	+	C/T
rs4706749	79804772	+	C/T
rs1415861	79805047	+	C/T
rs5877639	79805108	+	—/TTT
rs4055439	79805107	–	—/AAA

TABLE 6-continued

Polymorphic markers within the C06 region, between position 79,300,773 and 79,917,888 in NCBI Build 36. Shown is marker ID (rs-names), position in Build 36, strand and polymorphism type, where (—/N), N being any nucleotide or a plurality of nucleotides, corresponding to an insertion/deletion polymorphism (i.e. either the nucleotide(s) is present or not, as indicated).

Marker ID	Position Build 36	Strand	Polymorphism
rs35633350	79805108	+	—/TTT
rs34124549	79805944	+	—/A
rs11758432	79806313	+	C/T
rs6454094	79806528	+	C/T
rs9361482	79807104	+	C/T
rs35197393	79807335	+	—/T
rs34887019	79807963	+	—/T
rs9343862	79808197	+	C/G
rs35686657	79809315	–	C/T
rs9343863	79809511	+	C/T
rs2050662	79809792	+	C/G
rs9361483	79810005	+	C/T
rs2050663	79810113	+	C/T
rs7739298	79811079	+	A/G
rs35594811	79811779	+	A/C
rs9448616	79813653	+	A/G
rs34896515	79814085	+	—/C
rs13204088	79814157	+	A/C
rs34581263	79814707	+	—/G
rs34999680	79814872	+	—/C
rs9361484	79814937	+	A/C
rs9352686	79814942	+	G/T
rs34193659	79815383	+	—/C
rs28404148	79815386	+	A/C
rs34818907	79815757	+	—/C
rs9361485	79816451	+	C/T
rs35355402	79817319	+	—/C
rs4706080	79817716	+	C/T
rs9361486	79818479	+	C/T
rs2152951	79818891	+	A/G
rs35469490	79819211	+	—/C
rs9448617	79819766	+	A/G
rs12182597	79819707	+	A/G
rs11968462	79819711	+	C/T
rs9350801	79819985	+	C/G
rs9448618	79820526	+	G/T
rs6928507	79820970	+	A/C
rs6928518	79820984	+	A/G
rs6929315	79821334	+	C/T
rs9343865	79821914	+	A/T
rs11760038	79822663	+	A/G
rs34192988	79822723	+	—/G
rs9969106	79822922	+	G/T
rs6454095	79823093	+	C/T
rs12110918	79823270	+	A/G
rs9443640	79823496	+	C/T
rs28393972	79823721	+	C/G
rs28587408	79823722	+	G/T
rs11292616	79823758	+	—/A
rs6915558	79825775	+	A/T
rs10528595	79826027	+	—/ TATATA
			—/ TATATAT
			—/ ATATATA
rs10631256	79826038	+	—/ATAT
rs34479070	79826039	+	—/ATAT
rs10668885	79826050	+	—/ ATATAT
			—/ AT
rs10668886	79826051	+	—/ ATATAT
			—/ AT/TATA
			—/ TATATA
rs35594282	79826052	+	—/ TATATA
			—/ TATA
rs34850134	79826053	+	—/ ATATAT
			—/ ATATAT
rs10943614	79826062	+	A/T

TABLE 6-continued

Polymorphic markers within the C06 region, between position 79,300,773 and 79,917,888 in NCBI Build 36. Shown is marker ID (rs-names), position in Build 36, strand and polymorphism type, where (—/N), N being any nucleotide or a plurality of nucleotides, corresponding to an insertion/deletion polymorphism (i.e. either the nucleotide(s) is present or not, as indicated).

Marker ID	Position Build 36	Strand	Polymorphism
rs7753638	79826260	+	C/T
rs6917206	79826433	+	C/G
rs11295038	79826554	+	—/A
rs7454519	79827581	+	C/G
rs9343867	79829072	+	G/T
rs6925447	79829270	+	C/T
rs9448620	79829965	+	C/G
rs10688271	79832242	+	—/CA
rs1547731	79832823	+	A/G
rs9352688	79832882	+	A/G
rs28562383	79833897	+	A/T
rs9448623	79834479	+	C/T
rs9968921	79835098	+	A/G
rs34949474	79835636	+	A/C
rs10455120	79836486	+	G/T
rs12529731	79837484	+	A/G
rs9352689	79839533	+	C/T
rs9361488	79839593	+	C/T
rs7744876	79839756	+	A/G
rs9352690	79840271	+	A/C
rs3857447	79840542	+	C/T
rs28361939	79840905	+	G/T
rs13216433	79841107	+	G/T
rs9343869	79841140	+	C/G
rs34915363	79841523	+	—/T
rs9448624	79841582	+	G/T
rs35664126	79841883	+	—/A
rs9443641	79842023	+	A/C
rs9352691	79842326	+	C/T
rs34821012	79843195	+	—/A
rs3812161	79843364	–	G/T
rs12526671	79844774	+	C/G
rs1413967	79845731	–	A/C
rs9343870	79846192	+	G/T
rs7753531	79846715	+	A/C
rs1413969	79847701	–	C/T
rs1413968	79847761	–	C/T
rs4055438	79848331	+	—/CACA
rs1415860	79848500	–	C/T
rs13212056	79849331	+	A/C
rs7776432	79851211	+	G/T
rs36017295	79851212	+	GC/TT
rs7776138	79851212	+	C/T
rs1415859	79851577	–	C/T
rs35716913	79851705	+	—/T
rs12154147	79852063	+	C/T
rs12212124	79852485	+	C/T
rs9359364	79852711	+	A/G
rs9443642	79853322	+	G/T
rs9448625	79853356	+	C/T
rs9352693	79854791	+	A/T
rs9443643	79855557	+	A/G
rs12664690	79856551	+	C/T
rs9352694	79857537	+	A/G
rs13206256	79860401	+	A/G
rs11963526	79860546	+	A/G
rs4706750	79862281	+	A/G
rs7773757	79862756	+	A/G
rs5877640	79865118	+	—/T
rs35313660	79865119	+	—/T
rs12193154	79866583	+	C/T
rs7767100	79867252	+	A/C
rs9443644	79867363	+	A/G
rs7767711	79867419	+	A/G
rs12214911	79867844	+	C/T
rs4507549	79868299	+	C/T
rs9448627	79868502	+	A/G
rs6899909	79868551	+	A/C
rs12660124	79868563	+	A/G
rs28379467	79868586	+	A/C

TABLE 6-continued

Polymorphic markers within the C06 region, between position 79,300,773 and 79,917,888 in NCBI Build 36. Shown is marker ID (rs-names), position in Build 36, strand and polymorphism type, where (—/N), N being any nucleotide or a plurality of nucleotides, corresponding to an insertion/deletion polymorphism (i.e. either the nucleotide(s) is present or not, as indicated).

Marker ID	Position Build 36	Strand	Polymorphism
rs9689135	79868589	+	A/C
rs9689136	79868593	+	A/C
rs6906253	79869724	+	A/C
rs34349727	79870222	+	—/T
rs1538232	79870555	+	C/T
rs7749916	79870911	+	A/G
rs12195753	79872084	+	C/T
rs34664515	79872349	+	—/C
rs12197385	79872695	+	A/C
rs11968729	79872968	+	A/T
rs9361489	79873504	+	C/T
rs4144106	79873950	+	A/C
rs5877641	79874047	+	—/TTT
rs35186945	79874048	+	—/TTT
rs5877642	79874056	+	—/TTT
rs34582407	79874057	+	—/TT
rs4055440	79874065	+	—/T/TT/TTT
rs34285696	79874066	+	—/TT
rs5877644	79874142	+	—/A
rs5877645	79874154	+	—/A
rs949846	79874315	–	A/G
rs35175594	79874354	+	—/T
rs6916081	79874571	+	C/T
rs9341758	79876533	+	C/T
rs9343871	79876838	+	C/T
rs11967829	79876870	+	A/T
rs4460185	79877129	+	A/G
rs12203969	79877616	+	G/T
rs35921542	79878727	+	—/T
rs1415310	79879033	+	C/T
rs34887350	79879491	+	—/CA
rs9443645	79879643	+	C/T
rs35532958	79879775	+	—/G
rs12208017	79880090	+	G/T
rs10943616	79880260	+	A/G
rs6940949	79880754	+	A/G
rs6904124	79881799	+	C/G
rs34131532	79882366	+	—/GA
rs34222053	79882584	+	—/G
rs9361491	79882867	+	C/T
rs9352696	79882949	+	A/T
rs34096134	79883539	+	—/A
rs13437410	79883867	+	C/G
rs1337128	79884042	+	A/G
rs1415311	79884599	+	A/C
rs9352697	79885302	+	G/T
rs6902186	79886779	+	A/T
rs6902217	79886841	+	A/G
rs35067617	79886856	+	—/A
rs34297827	79887590	+	—/A
rs7747226	79888212	+	A/G
rs7747540	79888379	+	G/T
rs1577793	79888739	+	A/G
rs34004133	79889589	+	—/G
rs9448636	79890158	+	C/T
rs9448637	79890797	+	C/G
rs6454096	79891729	+	A/G
rs7768264	79891856	+	C/G
rs7768535	79892231	+	C/T
rs11285425	79892473	+	—/T
rs9688601	79892482	+	C/T
rs11361003	79892488	+	—/T
rs11362933	79892493	+	—/T
rs12055857	79892585	+	A/G
rs12055858	79892634	+	A/G
rs9294129	79892802	+	A/C
rs9443647	79892908	+	C/G
rs34216559	79893168	+	—/A
rs3920791	79893453	–	G/T
rs1361043	79893786	–	A/G

TABLE 6-continued

Polymorphic markers within the C06 region, between position 79,300,773 and 79,917,888 in NCBI Build 36. Shown is marker ID (rs-names), position in Build 36, strand and polymorphism type, where (—/N), N being any nucleotide or a plurality of nucleotides, corresponding to an insertion/deletion polymorphism (i.e. either the nucleotide(s) is present or not, as indicated).

Marker ID	Position Build 36	Strand	Polymorphism
rs5877646	79893802	+	—/A
rs1577794	79894899	–	A/G
rs7771746	79895912	+	C/T
rs7751626	79895992	+	A/C
rs7751628	79895996	+	A/C
rs7751918	79896046	+	A/G
rs11757274	79896170	+	A/G
rs1832281	79896696	–	G/T
rs34002011	79897278	+	—/C
rs9448638	79897415	+	A/G
rs9448639	79897548	+	C/T
rs36080847	79897705	+	—/C
rs35178487	79897768	+	—/C
rs9448640	79898041	+	A/G
rs6938269	79898250	+	A/G
rs34749590	79898414	+	—/C
rs6900032	79898558	+	C/G
rs6899945	79898698	+	C/T
rs1856089	79898889	–	G/T
rs1856090	79899041	–	A/G
rs28793115	79899460	+	A/G
rs6906655	79900092	+	A/G
rs6929531	79900136	+	C/T
rs2210948	79900755	–	C/T
rs9359366	79900866	+	A/G
rs9343875	79901113	+	C/T
rs9343876	79901219	+	A/G
rs9448642	79901713	+	C/T
rs9341760	79901973	+	A/G
rs9361493	79903957	+	C/T
rs34851468	79903998	+	—/C
rs2321960	79904819	+	C/T
rs4547969	79905337	+	C/G
rs2321961	79905575	+	C/T
rs9361496	79905887	+	A/G
rs6922885	79906095	+	C/T
rs6900076	79906130	+	A/T
rs34635585	79906257	+	—/AA
rs12527205	79906518	+	C/T
rs6916942	79907146	+	A/G
rs13192783	79907675	+	G/T
rs35970033	79907754	+	—/GTGT
rs13207216	79907776	+	C/G
rs9448644	79909382	+	A/C
rs956550	79909459	–	A/G/T
rs11450125	79909773	+	—/A
rs35277763	79909871	+	—/C
rs9443648	79910324	+	A/G
rs17785485	79910945	+	C/T
rs17723508	79911083	+	A/G
rs9448645	79911477	+	A/G
rs6904674	79912150	+	A/C
rs28369551	79912158	+	A/T
rs6933121	79912963	+	C/T
rs7768622	79913223	+	G/T
rs10484946	79913349	–	A/G
rs12196543	79914619	+	A/G
rs9448647	79915916	+	A/T
rs9352701	79916596	+	A/G
rs9361497	79916649	+	C/T
rs9448648	79916948	+	A/G
rs9294130	79917888	+	A/G

Example 2

Further analysis of marker rs11228565, which is located within LD Block C11 and in LD with rs10896450 (D'=1, r^2=0.25), was performed, with results as shown in Table 7.

Highly significant association of the A allele of rs11228565 to prostate cancer was revealed, with combined P-value for all cohorts genome-wide significant ($P=6.7\times10^{-12}$). The odds ratio (OR) for rs11228565 after adjusting for rs10896450 was determined to be 1.16 (P value=4.9 E-04) when using results for all populations except Finland (i.e. where we have results for both markers rs11228565 and rs10896450 in: Iceland, Chicago, Netherlands, Nashville and Spain cohorts.

TABLE 7

Association of rs11228565 with prostate cancer.

Study population	Marker	Allele	P value	OR	Cases (n)	Case Freq.	Controls (n)	Control Freq.
Iceland	rs11228565	A	7.72E−03	1.23	1784	0.209	771	0.176
The Netherlands	rs11228565	A	2.15E−02	1.17	992	0.229	1781	0.202
Spain	rs11228565	A	3.42E−01	1.09	394	0.240	1399	0.224
Finland	rs11228565	A	3.22E−06	1.30	2643	0.210	1689	0.169
Chicago, USA	rs11228565	A	8.00E−02	1.16	755	0.235	878	0.210
Nashville, USA	rs11228565	A	8.49E−05	1.43	592	0.291	685	0.223
All combined	rs11228565	A	6.70E−12	1.23	7160	—	7203	—

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tgcctatttt tgtctgtttt tgtgactttt tctttctctt cttccttttc atattcactt 240

aatatttcaa tttttaaagt acttttcatg ttgtgaatag ttttgtataa acccacgaar 300

tatatttgag tagtgttgtt tgaactctaa cctgataaag tttcacttcc tcaacctgcc 360

ctcaaaatat ggccagggtg gacatgttcc aaattgaatt actccataaa aacagtcaga 420

atctcagata aacagtgact tccaaatatt aaaaataaat atgtgaataa ttttaattaa 480

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tgtaacatag tttggcagat tttatatgag ctggccacag ctttttaata ggtatgtaac 540

tccctttaa acaaaggatt tcatagacaa aatgttctac attatatgaa tttctcaaa 599

<210> SEQ ID NO 21
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 21

tcttgaatgg gattgtgtct gtgttgttat aaatatttta tattcagaac aagagcttga 60

atctagtcta ttgtgaagga tgaaagagaa gtattttatc agggaagcca cttatcagat 120

ttatgttttc taaaaatcaa tgtggttgtt ttgtttaaag caccacagat tctttcacat 180

ttctcctact aatgggtggg atctatgttc cttcctcttg aatctgggca ggcttgtaac 240

tgcttcaacc aatatggatt gacagaagtg atactatttc actttcaaag cccaaggtcr 300

tatatcttct acctggttct ctttggaggc tcactctgga ataagccaaa ttccacttaa 360

ggattccaat tacaccattc tggagaagtc tgtaggtaca tctgtcagca gttcaaacct 420

tctagtcatc tctgccaaga caccagacag gtgagttaag gagcttctag aggatttcag 480

tctccagcca tttgtcaccc ccagctgttt aaatatcccc aaatgaaacc tcacacactg 540

aggagtagag acaagccatc cctactatac cccatcccag tttctgactc ctagaatcc 599

<210> SEQ ID NO 22
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 22

aacaatctgt ttgccaagga gcttcctgag agcttcaaaa gcagtggtag ttaaggcctg 60

cctcttgaag atagtcctga tccaggtgta ccaaccacat aaaaaagaca gtccacaaag 120

gtctcagtga tttatgctca gtccctttca ttaatattgc caatcatgta atccattctt 180

taccccttga aaagaaggga gggtagaagt gggggtagtg tagaagaaat agtgggagct 240

ctgttcccag ttcttctgaa ggagctgttc ttgttttgtg agtctaagtg aaaacattay 300

gtcaaaaaga atatagcttt ttctttgctc tctgctctgt ggagccaggc agggtaggaa 360

aaggagattc cagggagcta agaatttaaa gccagagtga ctgtcaacat tcccatagtg 420

aaacgcagct ccccttcact agtcctaaat ggtgccctat agaaccctgg aagaccttcc 480

cgggggcacg tcacaacctc actgacgcaa aatgtcctct ttgggactac cagaagacac 540

catgtagtaa cctttgtagg tagatggctg ctgagtcact ataatgaaca tctaaaatt 599

<210> SEQ ID NO 23
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 23

cagctcccct tcactagtcc taaatggtgc cctatagaac cctggaagac cttcccgggg 60

gcacgtcaca acctcactga cgcaaaatgt cctctttggg actaccagaa gacaccatgt 120

agtaaccttt gtaggtagat ggctgctgag tcactataat gaacatctaa aatttaacat 180

cttctccttt tactttgtat taccaatgat ttatttttta ttctttttaa aaagaataca 240

atataacttg gaaaagaatt ggctagatac agctcagtgg acttaaaaca atgtgctatr 300

tttgaacaac atcaaattat ttttgaaaac cttgccaagt gacttcaata agatgagaac 360

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tattaacatg aacttttaaa acagcaaatt tcaaacattt tttagatgtt ttctgcactg 420

gatgttgtag agtactattt agatcctccc tgaagaccaa ggcattcttt tcctcaggtg 480

ctaagaatct tgcctactga tgactcacag ctgagtccac ctacaggcat ttcccttcac 540

tgaaaaaagt tgtttccccc aatcctgcac aaactatgtc ccatcctgga aggcagcca 599

<210> SEQ ID NO 24
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 24

ctgccaacag tcgtgttatt aaaacaataa cttgcgaatt tcaagctcaa aattcttaca 60

tgatttctca ttcaatacaa aataaaatac aatctcatca acccagaatt caaagtcctc 120

taccatatga aatagtcttc ttaacaacta tttgctgctg gacacacaca aacatccaca 180

caccatactc ctcttaattc cttcagtcta cacttttaga actctgtgtg gcttttgtta 240

agctattgtt taagctaaaa gctcttcttc caagccatct cttccttaac agttcaaatr 300

ccacttttc ttacatccat tagttgattt ttttcttgaa tttttattgt actttaattc 360

ttcctttatt ttgatgctga acactgcttt ttctataaca tacgtgagtg catacatatg 420

tattatatat gcatttttta gctccttaaa agttaagaac tatgtcttag taatcttgac 480

atagaagatt ctaaaaatag tatttattaa tttctattgc aagttggtaa taaggcaatg 540

atattttcca taaagaaaaa tgagagtaga actttatttt agtttgttga tattttgac 599

<210> SEQ ID NO 25
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 25

aatggtagag ttagaaaaca agggcatggg atgcatccca agtctttcat ccttttaata 60

ttcatagaca accaagagcc aactacatac atcaattcaa gattaaaaac atgaaagttg 120

aaaggaaaag aaatctataa gcaattacca ccttccaagt cttatgttga tattacagag 180

tatcttggga gttggtttga ttaaggaaat acgtggtgct ccattaaaat ttcttactta 240

tttttattac actctcactt gccctaatga aaataatttt ctttctgttt caggcctgts 300

catcttttgt taaagttaaa tacgccatta gtaatataaa atcaaataac cagatagatg 360

ataaagccat aaagagacag acagagagat aacagtttca aatgctttta gagtctacta 420

acattggtga atttctaaga tttagttaat acatcaggaa actgagaaat tagaccacct 480

cttcattttc tttgaaacct agttggcata ttgatctgtg ttgggttgca ggtttaaaaa 540

ggagccatac gccaattagg actgtgacag tggaataact cttcctgtat accccatta 599

<210> SEQ ID NO 26
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 26

tctaatatac cactggaatt aaataaatag tgtcatatag aaggaattac attggtgtag 60

aggcctaggt tcttgcccca atctacagtt gccatctaac tacattgtac acattaccat 120

catgaaactc gataaataac tactcagatt gataataagt aaaagccatt agactttcct 180

tcaaaaatac attgagtact ctttttcaca ctcttcaatc ttcaatgttc tcaccagttg 240

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ctctgtgtct tgcagatgaa tctttgtttg ttttagttct ttttagttct tttcttctty 300

ctaggatgtt tgtccatatt aacaattcct tccttttata acagctccct aaagaaactc 360

tttggtcttt tctcccattg caccctcttc acattggaat caaattgcct ggttttccat 420

ctgcataaaa ttatctctga aatctgaatt ctacatatca cccaggaccc gttcctatgc 480

tatatttttc atgagatttt tactggtcct cccagctagt gcttcctcca ctcatggaac 540

ttccatagca ttcaatccat gcctctttta agataattac aattttctgt gaatatgca 599

<210> SEQ ID NO 27
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 27

gcagaatttt aaaaaataaa agatggccaa taaactagac caaaggacaa aaagataatc 60

ggtgaaacct cacctcaaag atggcagagg acaggagttt aagaaaacaa agggacagtt 120

gaatggacac taaggagaaa gagaggttcc caaagaaggg atataaacac ttcctgagaa 180

atccagagat gttcaacccc tagaaataag aagaaagaca cattgggaat aggtgtttaa 240

gatgtagatg aggcaagatc aataaaatag aggcacatat gtgccacgaa gggacactcy 300

atgtgaatta taataggcaa cttatggctc acctcaagaa cagttatgtc cattgttctg 360

aactttgaca tatgcaccca cattattgaa cttacaaagc ttaaggagtg gaaagagatc 420

aaatgcattt ggaactgatg ataaacgtat gtgacagaat gtgcctgtac tttgggtgat 480

atcattgagt gaatacacat atagaagaaa gctttaattt tcatttttg ccaaaactca 540

tgtcaacttt aaaatatgct catatttcat taacaagaaa acaaaatatc ctgtcataa 599

<210> SEQ ID NO 28
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 28

cagtctaatt caaccccaag gcaggtgaat gttaagagat tgaaggctgc tgccaacact 60

tacagctgag aaatccttgt atctgcctcc tgtgggaaaa gagaaatgga cccagagtga 120

ttctatttct ccttccaaat cttgagcaag ggcttcctat tggcagaact ctaaatgcat 180

ttagaatact gagagcaggg gagttcagga gttgcagttc cttggcttct agcctctgtg 240

atacagagaa gagcctaaaa gagattgtca gtgtgatggt tgtggtggtg gggggaggar 300

gaaaatgcga cttgccaaaa gaacccaata tttagcaaaa ccttcccttt cattctgata 360

agtgtgttta accaaagatg aatacgtctt tttctaggaa ctagaaagag ggaatagttt 420

ggcatattga atatgcttga tttaagttgg cattaatatt agatagcaac tctctggctt 480

aagtgatgaa aatactgaga tatacattaa aaacacaccc aaagctaagt taaggcatag 540

attgcttttt cataaagagg aattgtacaa ttttataagc tattacattg ttatgctta 599

<210> SEQ ID NO 29
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 29

cttagattat agaattatat gtgaatatgc ttttggctct tacaccatta atgttacatg 60

taatcaaaag taattaaatt ttcaaaatta gtaaaaccac tcagttaagc aatgtaagca 120

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tacattagct gataatcatt tacaatgcca attgcatcct gaggctgtta ttgacatgtc 180

agcagagcat atgatagagt tgtttttctg ccagtactaa tccagaaaca atgtaaggtt 240

gccaatgcag atgggattgt atttgtagaa tggagcaatt cccataagag atttttgccr 300

tactaacagt cgctaggact tcctcagttt tctcctgtgc caggtggcag tagccaccaa 360

cagcatttgg gcactctgcc ccaccacctc cctcctctcc tgtggggaca tccaataaag 420

atgagaaaga cgtgctttgg gcaccaataa attagggaca acaaaatgtg atattctgga 480

agaaatgtca agtcaaaaaa tactgggaaa tctcagcatt tcttcacatt tatttgtatg 540

gtctattaat taatataagt atcataccat ttggctgtgc tttgatgttt gtcagtgac 599

<210> SEQ ID NO 30
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 30

cccagagaca tgcacctcca gaatactcag agccaatgat tggcccaact gaagacaatt 60

ttgaggggcc actgggcttc cattgtagtt aaaaatctgc agaattctac ttagttctcc 120

tgctttccac atgcattcca tgggcacttt tcaaataatt ccctgaacac taaactctgt 180

cccagagact gctcctaggg aatccaactg gcaatgcttt tcatgcaact ccatccattg 240

ttttcttcat ttttctctta ttgggcccaa aaatatgcct cttgcatttc cacttaccar 300

tccttcttct gtcctcagaa ccaacacaaa taggaatatt ctgatgttaa tttgaaaatt 360

cctttaaata tttgtttatt ggaatttctt gaaacatacc tgatcaatgc aatgacaaca 420

gttaactagg tcaatattta taccaacata taacttgcaa ttctttctcc aagaattaaa 480

atacaaattc attgaaaact gctaaaaaac taatcgatac tttccaacat atttatactg 540

ttataagacc tatttcatca cttggaccct ccttttctaa catagctgtc aaaagaatg 599

<210> SEQ ID NO 31
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 31

ttataggtgt caatagattg agtgatgtgc cttaggcaca tgaaaaccag gctttccaga 60

tgcagctctg aggttaatgt ttcactgttg tatagcaact ttccatccga gggttcctaa 120

gagctttata actttacaaa caatctaatg tctttgaagt caatactctt cctttcctaa 180

atgaacataa attcttctcg aattcaccag ggaaaaaaag cacaatgact gctccattgc 240

ttcatcagtg ttagctgtgc ctgacactgg actccagctg cacttttta tataactgty 300

atagctctta tcacattatg gcaaaattat taatttatac atctgtctcc ccaaatagcc 360

agcaggcaac ttgatggcaa agactgtgtc ttattcacct tggtacagtt tcagttcaac 420

aaccatttaa tgagcacgta ctctgtgcca ggattcaagc tagatggtgt caggttataa 480

agacaaatga aacacagcac aggcccttga ggatgctgtg gacaagtgga ggagacaggt 540

acattaattg ttcatttcag cagagtgtgg aagaaactac aatggatatt taaagccct 599

<210> SEQ ID NO 32
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 32

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aagcacaatg actgctccat tgcttcatca gtgttagctg tgcctgacac tggactccag 60

ctgcactttt ttatataact gttatagctc ttatcacatt atggcaaaat tattaattta 120

tacatctgtc tccccaaata gccagcaggc aacttgatgg caaagactgt gtcttattca 180

ccttggtaca gtttcagttc aacaaccatt taatgagcac gtactctgtg ccaggattca 240

agctagatgg tgtcaggtta taaagacaaa tgaaacacag cacaggccct tgaggatgcy 300

gtggacaagt ggaggagaca ggtacattaa ttgttcattt cagcagagtg tggaagaaac 360

tacaatggat atttaaagcc ctgcatagac tttcttctgc ctctaatact ctacccccat 420

cttctaatac tctccccatt gcttactgga ctgtaggtac attggttttc ttgctgtttt 480

tttgaacata accagcatgt catcacatca aaatatttga actttccttt atggaatagt 540

gttctcctac atattcacgt ggcttacccc tgcacatctt tgagtgtttt taattctgc 599

<210> SEQ ID NO 33
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 33

tatgtatatt gggtttgagc caagtaacta gtatgctgcc cagataatag acccttcagt 60

ctcactctca agggcagcag ttgggggaag gagttgtttc tagggcagct ggagcgctga 120

tgtgatgggc attggaatac actgagctag agcatgggct ttgcagtcag gaaaatatgg 180

ctctgctagt ttaaatgcta tgtaatctca gttaggcaag ttagcatctc taaatatttc 240

aattcccttc ctgtgggaaa aaaaatgaat actttcattg tgtcataccc attaaatagy 300

gttagatctg tgaaaggctt agcagagttt cagactcata gcaggtgcct aaggagagag 360

aattagctaa ttaaaagtat tataagcata ttacaattat aatacactaa tgaagtataa 420

aagtaatcta gtcgttcata tattctttga ctttttgcca cgtaaaacta taagacagat 480

ctgagaattg ccctgagaga taactcagca tgctgtgaaa atgaaacaaa ttggtatagg 540

ttgataatct ccctgaaaaa aaggattccc aagcaccata ggtgagaagg gcagtgtaa 599

<210> SEQ ID NO 34
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 34

aaatatgaca cattatttga aagatcctaa tgtgttagtc aaaatctttt tatgacagca 60

aggattttaa ttagccatac attggtaatt tcagttagtc atacattttg taaataaaaa 120

cggaagtgag gatggccaaa taggaacagc tccagtctat ggctcccagt gtgagtgaca 180

cagaaggcaa atgatttcta catttccaac agaggtacca ggttcatctc actggggatt 240

gtccgacagt gggtgcagga cagtgggtgc agtgcaccga gcatgagctg aagcagggck 300

gtgagctgaa gcaggcaagg aatcgcctca cctgggaagt gcaaggggtc agggaatacg 360

ctttcctagc caaggaaagg ggtgacagac agcacctgga aaattgggtc actcccaccc 420

taatactgca cttttctcat ggtcttagca aacggtatgc caggagatta tatcccacgc 480

ctggctcgga gggtcctacg cccagggatc ctcactcatt gcaagcacag cagtctgaga 540

tcaaactgca aggtggcagc gagggtgggg gtggggcgcc gaccattgct gaggcttca 599

<210> SEQ ID NO 35
<211> LENGTH: 599
<212> TYPE: DNA

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 35

tgatgaaaac acctaactca ccttagaaga aagtatttgg catgaggaag cactcaaaac 60

ccatcactaa ttgctctaaa atcatatgtt caataggcta tgaattaagc taacttgtca 120

caattcctcc tatcatcact tccacatttc tcttgatgat attaacaact tcatagaatc 180

attcctctgt aatagtttgg tggaagaatc tgctatataa ataaatgcat gttatagaga 240

cactttgaaa agctcatgtc gcctttatct gacagcacct ctgttcagaa aagtggaaam 300

ctggctctat gagtatatgc attcatgagc tcttgattga aaggggtcag tttcagaaat 360

ctctgagttg gaggtcttgg gcctgagcct attaagataa ataactcccc cagggtaact 420

catcaatgag gagacttcag cagttaaatt ccctagacta agtctcatgt tctcactcag 480

cacactaacc catgcacagc taaattatct catccacaat ttcaattttt gattcaacta 540

aaaaatacat gcctataaag ataagtcttc aagtaagcca gacacacggt agtaggaag 599

<210> SEQ ID NO 36
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 36

tcatctgaaa cttctgtaaa tgctgtgaga agagcttggg gaagaagaga cattgaactc 60

tcttcaaaca taaccatgaa atgtgaagtc accctaccaa aaggagcctc tcatctatat 120

aaaaatgaaa aacaaccagg caaaaaagaa aaaaaaaaca ttttgctctt caagttaaaa 180

taataagaat caaaaggtaa ggctgagtcc tgggaagtat gttatataaa tatacaacac 240

aagagagacc attatgttaa gaaggctcca gcaagaatta tagctgcttt cctgtttacr 300

tgacaatcta cctatgacaa aagttttcca ccctttctct tattgtagac ttttaacaaa 360

atctcatgct catactcttc tccatcattt aaaactcaac tcactggcat cctcactaca 420

atgccttacc tttgaaatgt acatcatgta aacttacagc caaaacgttg tggaataagg 480

agtgcagatt agaaaacttc ttaatttcaa tgcttgtcct aatactgtta ctaaaatgaa 540

tgaaaagtat attcctgggc aggcacaggt gggcagatca tttgagtcca ggggtttga 599

<210> SEQ ID NO 37
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 37

gagcccactt cctcattcat agacagctgt cttttccctg tgtcctccca tgatggaagg 60

aacaagacag aaccccgctg tctcttttat aagagcacta atcccattca tgagggctcc 120

acctttatca gttaatcagc tcccaaaggc cccacttcca aataccgtca cactggggat 180

tagatttcaa catatgaata tggagcaggg aggggacaca aacatttagt atattgcaag 240

aactattttt cttgctgttt catgatgtaa ggtaagttct cttccgctgc tcctgtggas 300

agtacctcct actggtggtg tcatggtggc tgaggatgtc tgttatgaag caaaacagag 360

aagagaagag gcctcttttt tggctgtatt cagttaaagg agtcctacaa cagtgttgct 420

catactacaa ggtgttaaag aagttaatta aatagtcctc tcagcattca ctcataatct 480

tctctggaac cagaacttag acaagcatcc tgagtgatgg aaacattttc atggaggaag 540

gaccagacat tttgagaaca ttttatgtct atagtaaaag agaagagaaa acaggaata 599

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<210> SEQ ID NO 38
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 38

aaacactgac aaaaaaaaaa aaaaaaagac ctggcttcct tggctctgca tgtagataat 60

ctccctcagc taattacagt aaatgccaaa gatctaacat ctttcctgca gacccacaag 120

gaagatatat gagaaaatac tgtaggatgc ttgcaagact gaatttccaa agcagcttta 180

aagggaatta taaggaagat gttagaacat taggggaaaa tcagtgctgt attgcaaagg 240

aaatgtttaa ttgtaaagag ataactgttt ttttgtacat gtgttccaac aggagattcr 300

tgaaaactta actgaactta acatggttat atgagacagc aagtgacatg aaggagcaga 360

ccaccaagat tttggtagta tatcccagtg ttcctttgtc attggcaact tgttctcagt 420

aaaatatata tatatatata tatatatata tatatatata tatatatata tgtttattcc 480

tcctccctca taattattaa gtgaaactcc cagttaccaa agttagttat tattttgatt 540

aatttggcat taaaccatta ggagtgatat acttaactct tcccatggga atttttcct 599

<210> SEQ ID NO 39
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 39

cattttgccc ctgccctaga gatctgtgga actttgaact tgagagtgat aatttagggt 60

atctggcaga agaaacttct aagaagcaac gcgttcaaga ggtgacagag cataaaagtt 120

tagaaaattt gcagcttgac aatgcagtag aaaagaagaa cccattttct ggggagaaat 180

tggaaattgt gttttattaa tagacttcgg agtatgtatg gaaatgcctg gatgtccagg 240

gagaagtctg ctgcaggagc agacctctca tggagagcct ctgctagggc agtatggaar 300

ggaaatgcgg gattggaacc ccaacacaga gtccccactg gggcactgcc tagtagagct 360

gtgagaacag ggccaccatt ctctaggccc cagaatggta gatccaccaa tggcttgcac 420

catgcacctg gaaaagctgc aggcactcaa caccagccca tgaaagcagc caggttgagg 480

gctgtaccct gcaaagccac agaggcagag ttgcccaagg tgtaggagcc tacctcttgc 540

atcaacgtga cctggatgtg agacatggag tcaaacgaca tcattttgga acttaaagg 599

<210> SEQ ID NO 40
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 40

agatgagttt gaagggttaa aatgtcagac attatttgga aatcaaaaaa tcattatttt 60

cttgataatt agaaaataga ggcagggtta aataatgact tatttatatc taagataact 120

taggctcatt ttctccttta ttgaaataat acctgcagtg atagatattt ccagaagtga 180

gagatatatg tgtatttgta tatatttttc ccagagctta ttattttgca tattaccact 240

acatagagat gttgtaaaag aactaagagc aaactatggc aaaggcagat aatgaagggr 300

taaaattaat gtttaaaata gaatcctcaa caatcggtga caataaaggt aaatgataag 360

tgaaattgta tatttcagta atgtaagcat ataaaagaag atagcttttg aaagattgaa 420

ttaccctcat tcattctgaa gaaaaaaaat aaagttttat tatacataga tgctatggag 480

-continued

tggaactcaa ttgtgggtga tcataaaagt atcttttact tgctgtccca agcatttgga 540

agtgtaacaa attccaagat tgggctgcag agcctcttta aaaagggtat ccacatagt 599

<210> SEQ ID NO 41
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 41

aagagtttat ttgggacaag attgaggact gtggcctggg acacacttcc aaagtgcctt 60

gggaagtgct ctggcaaaca aaggagagac tcaagttttt aatgaaaaac gaggcaaatc 120

agcagaaggg gaaactataa aagtagttca tcaggaattc tcactggttt acagaagtaa 180

ctttgattag caattggcta tacattgtta aattacaggg taagagttat ggtggtaaga 240

gtatgttatt ttatggctac ttggtattag ttagtagcca caaaatgctc acacagcaas 300

tggtttcaag aggtaatggt actcagttca atggggagtg aaatttgtta cattttaaat 360

gcctctttgg gactgaaaat gtaaaggagc tctcattgct cagataattt ttttctttct 420

cacattcaat atttattcaa caaatgccta ttgaatgaac ggatggatag atggtgaaag 480

ataaaatgaa aaaaattcaa tggtgtgcaa tatcaaagaa acatcagctt ggagccagac 540

atacagggat tcaaatttcc tatctgccac taactagctg tgtaatcttg ggaaataac 599

<210> SEQ ID NO 42
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 42

gagatgtatt aatggtgttg gttttatagg acccttagc tttgattctg ggtgcatatg 60

gcaatgtagc ctctatatgg tttctttggc tgtaaacagt atgagtaaca tctgtggttt 120

cctaggtggt ttaggctcta attattagtg gaggctatgg tgaagttttt ctgggggcag 180

ggatggcagg tgggtccata tctggtcccc attggtggaa gcagtgggct gagcatgctt 240

actcttgggc ccaagcatag cagatgctgg cacttgtgtt agtgggataa agtaggccar 300

ttcttgagcc tgtagtggct gcagtgggct gggtgggtaa atgggttccc atgtccccga 360

gaagtcaacg tggtatcagt gaagccagta gcagtggtgg gatgactctc tgggtcctga 420

gcactgcaca ttggtattgg tggtggttgt atgcaaggtt gccagtcaca gccccagaca 480

tacagttctc aaatgttcct gctctccaca gcagcagcac cacagcatca cacagaagca 540

ggtaggaacc acacatttca tgtgctagcc tgtgtatata ggctatgcta ccaaaatat 599

<210> SEQ ID NO 43
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 43

tgctctccac agcagcagca ccacagcatc acacagaagc aggtaggaac cacacatttc 60

atgtgctagc ctgtgtatat aggctatgct accaaaatat gtcatatgat aacaagtatt 120

agtgaaggta tgaggaaatt ggaagtattg tatatcatca gtgtaaatgt aaaatgacac 180

aactgctata gaaaacagta tggtggttct gtaaaaaatt aaaaatagaa cagcatatga 240

tccagcagtc ctagttttag atatttatcc aaaagaattg aatacaggat ctcaaaaagw 300

tgtttgcatt ctcacgttca ttgcagcact attcacaata gccaatatgt ggagacaacc 360

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taaatgccca tcaacagatg aatggataat gaatatgtag tatatacaga aaatcctgtc 420

atatctacaa catggatgaa ccttaaggtt atgctaagtg agacagctca tcgtattagg 480

acaaatactg catgcttcca tttatatgag gtatctaaag gagtcaaact catagaagca 540

gaaagtagaa tgacagttgc caggggttat ggggagggga aaatgaagag ttgctattt 599

<210> SEQ ID NO 44
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 44

atagaaaaag aaagtagatt agttgccatg ggatctggag aaggtgagat tgagactaac 60

tgctaataat taccaggttt ctttttgac atgatgaaaa tgtctggaat gaaatagtgg 120

tgatgtttgt acaacatata agtaaactaa aaatcactat attgtgcatt ttacaataat 180

gaatgttgtg tgaattgtgt ctcaatttaa aaacttttg aggtatattg tttaatttgc 240

aaaaacagat ggtctctggc ttatggtagt ttaacataca atttttgac cttatgatas 300

gtttattaag gtattaagta cattttgac ttatgagttt atcaggatgt actccatcat 360

aagtcaagga acatcgatat gtggtgatgt ttgtattatt gtttgaaatt tattttcata 420

ttaattctct tataatcaaa gaaactgtgt attatttaaa tcttttgaca tttgttgaaa 480

tttaatttat atactagtat atgatccatt tggtcgatag tttataatta taaaaatgtg 540

cattcagttg tagttcatta tagtgatcta tatatgtcat ttaagtcaag tgtcttaat 599

<210> SEQ ID NO 45
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 45

gaaagtagat tagttgccat gggatctgga gaaggtgaga ttgagactaa ctgctaataa 60

ttaccaggtt tctttttga catgatgaaa atgtctggaa tgaaatagtg gtgatgtttg 120

tacaacatat aagtaaacta aaaatcacta tattgtgcat tttacaataa tgaatgttgt 180

gtgaattgtg tctcaattta aaaacttttt gaggtatatt gtttaatttg caaaaacaga 240

tggtctctgg cttatggtag tttaacatac aatttttga ccttatgata cgtttattar 300

ggtattaagt acatttttga cttatgagtt tatcaggatg tactccatca taagtcaagg 360

aacatcgata tgtggtgatg tttgtattat tgtttgaaat ttattttcat attaattctc 420

ttataatcaa agaaactgtg tattatttaa atcttttgac atttgttgaa atttaattta 480

tatactagta tatgatccat ttggtcgata gtttataatt ataaaaatgt gcattcagtt 540

gtagttcatt atagtgatct atatatgtca tttaagtcaa gtgtcttaat cacgttaat 599

<210> SEQ ID NO 46
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 46

cagttgtagt tcattatagt gatctatata tgtcatttaa gtcaagtgtc ttaatcacgt 60

taatcagaac atttataacc tgatttttg tgtccatgct ttactaatta ctgaaaatta 120

gaatttccca caatttgtat attgccatta gatatgtcat ttttgtttta ttggttttga 180

tgctacgtta ttttagtcac atacaaactt agaagtgttc tatctttcta tttgaccatt 240

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ttatcattag aaaacattct acccttattc ctgataatat tttttgccat aaaatctacm 300

ttgtcagaca ttagctttct tttgctaaat tttacatgct gtttattgtt ccattttcta 360

cattcaaatt ttgtctttat gtttagagtc agccttttaa aagcagcata tagttgattt 420

tctaaaaata tgagcctgac aatcattgcc tttcacttga aaattttaga ccatttatgt 480

ttaatatacc actaatatat ctcaacttaa acatatcatc ttattatttg tcccaccttg 540

tctattttct ctcttttctc accttctttt gaattaatca actattttat tatttcatt 599

<210> SEQ ID NO 47
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 47

cttataagtc catgtctgat tcactcaata tttgtttgtt tttatgtgtt ttttctcgtg 60

tgtgtgtgtg tgtgtgtgtg tgtgtgtgtg tgtacatgtg tgcctggtct tttctttgat 120

atgggtaagt tttttattca aaaatgagtg ttttgaaaga aaagttgcat aaataaattg 180

aagccttaga gaatgttatc tgcttccaaa gagtatttag tcatacttct gttagaaaga 240

gtagaagctg attgccttaa tccaacagga ttaatcactt ttaaaagaga gtttccaacy 300

ttgtgatggt ttatttctag tttcccatga ctcatagaat atagtccctc ccatatgaaa 360

gcctgggagg tttaccaagg cttctgctca ttttttttaat gtaaatgtat tacaatagaa 420

ataattcaaa gttctgctcc acttcctagt ctcttaacca caattttctg ctcagtctca 480

gcttctaaac tgctggttcc aaataagcaa atctctcaag gaaaaggcat tgcagaatat 540

tgggattatc tcaatgcatt tcccatctca ggaatcttgg ccttcaagcc ccattgcct 599

<210> SEQ ID NO 48
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 48

aaatttgcca tatgtgtatt atcttttgta aaatttttttc tgttggtaat tatctatgtc 60

ttttgctcat ttaaagaatt atatttataa aataaattca taggatggta aattctgttg 120

ctgtgcatgt atgaaaagta gttactatgg aaaattcctt tacaaacaat gctgggaaat 180

ttgcttcata aatgaatcct taattagctg caaaacttat ttgttaacaa tactggatac 240

tgtattacta gcattgagaa ttaccattat tctttagttg caaaatttct tatggtctgr 300

caacataata aattattcat tgccatggtt tgatgaattc tgattattta tacttgaata 360

tatatgttat gttactgcaa tgaaaaggcc atttattcag tactatctca tcatcttctc 420

tttctaggga ttcatcatga atatccataa tatggtttct aaaaatgcat gaaggaatca 480

gaggagacct gctaaccatg aaaagaagag catagcaata gagaaccaaa gtggcacaag 540

aatgatcatc tttgaataat ttagaatcaa ataacatcaa atcaacaaac acttattga 599

<210> SEQ ID NO 49
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 49

caaacaatgc tgggaaattt gcttcataaa tgaatcctta attagctgca aaacttattt 60

gttaacaata ctggatactg tattactagc attgagaatt accattattc tttagttgca 120

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aaatttctta tggtctggca acataataaa ttattcattg ccatggtttg atgaattctg 180

attatttata cttgaatata tatgttatgt tactgcaatg aaaaggccat ttattcagta 240

ctatctcatc atcttctctt tctagggatt catcatgaat atccataata tggtttctam 300

aaatgcatga aggaatcaga ggagacctgc taaccatgaa aagaagagca tagcaataga 360

gaaccaaagt ggcacaagaa tgatcatctt tgaataattt agaatcaaat aacatcaaat 420

caacaaacac ttattgaagc tctccatctt tccatccttg attcctgtgt tattcagcat 480

ttttggtagg tttccagcag gcagccttct ctcaaaagta ctgttaggtt gtaatgtttg 540

caagtgctgt cttcaggctc tcttactgct gatgagtatc aatcacataa aattgtgta 599

<210> SEQ ID NO 50
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 50

taaaaaagtc tgaaattttt tactcctaaa gcaccctatt tcttatttac ttctaacata 60

acctacaagt cactaaagca gttaggttag aaagaaaatg tctgcagtgt ctcatagagc 120

aaagacccct ccaaagactc cagactctgg gtgaagatta agagcaggcc agcaatatta 180

cactgtaata aatgacaact gtcaataaga agtaaaagta aaagggtagt aatggcatct 240

taaaaaggca actacatttt gctttcttgc tttctttata tgttatatcc tgccttttaw 300

cttttcctat cgaccctggg tttatccgta tgccaacctc acatattaaa agcactctaa 360

tgtctccaca aagaagtact tgtgtgcatt tatttatcta tgtatattaa acgaaactgg 420

ttttctttga cttcttaatc cttctcgtta ggtccttaat tctcaataaa gaatatcctt 480

taaaacaaaa ttggtctaca caaacataca ggcagtgcca cctaatggca gctaccattc 540

attttaaggc attcaaaccg gagagactgc tgtagtattt agatgtcttt gtgaacaaa 599

<210> SEQ ID NO 51
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 51

tagcataaaa tgaaagcaca ggacctcttg tttaaaatgc tgggaaaaaa acagtgctgt 60

tgaagtccta aaatataaag ctgtttcctt tcttccatga tctctctctt gacttcttgt 120

ggtgtctttt atttgttact tgtgacaatc taagttttaa aaactctgtt tttttatttt 180

ttaaattaaa aaaatagatt caggggccca tgtgcaggtt tattacatgg gtatattttg 240

tagtagtggg gtttggactt ctagtgtacc catcacctga atagtgaaca ttgtagcaaw 300

aggtactgtt tcactcctca ctccgttccc actttcctcc ctcttggagt ccccagtgtc 360

cattatttcc ctctgtagct ccatgtgtac ccattgttta tctcccactt ataagggaga 420

acatgcagtc ttgggttttc tgtttctgag ttattccact taggataata gcctccagct 480

ccatccatgt tactgcaaaa tacatgtttc attcttttgt gtggccatag caattttaaa 540

atataaggac atttaactag tatacaggat agtcaaaatt acacaatttc tcagacata 599

<210> SEQ ID NO 52
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 52

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cctgtgtgac tgcacaggtt gtgaacctag ccctgtttgt gaaatgtagt aggacaaaaa 60

aaatcactct tctttaatca gggataaaaa caagacttac atttattact tcccacatgc 120

tgaatggtag gttaagtcct tcacatacac tatctcattt aaccatcaaa taacagtttg 180

gggtaggtat tattaccttc atttacagag aaggaaatag gagattttag aaactaagtg 240

atttacccaa tatctattga ctaaaaggta gtggagtagg gattttaacc cgggtttgas 300

tgaccccaaa gcccagttaa tctactactt ccataaaacc atttagtgca gattttaaat 360

tacaaaatat ttttaaactg ttagtattag atatacacat ataataaata cctacatgct 420

aataagacca agtatgaatt aatgaaatag catgattcac agattaattt tttaaaatct 480

cttctggcct tctaatgtaa tatgacaagt ggaacacata tgtttatctc ctttacctcc 540

tgaggcttca ttaaaatgat gatagtgctt ttttaaggta taagccatca actacaaat 599

<210> SEQ ID NO 53
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 53

agcccagtta atctactact tccataaaac catttagtgc agattttaaa ttacaaaata 60

tttttaaact gttagtatta gatatacaca tataataaat acctacatgc taataagacc 120

aagtatgaat taatgaaata gcatgattca cagattaatt ttttaaaatc tcttctggcc 180

ttctaatgta atatgacaag tggaacacat atgtttatct cctttacctc ctgaggcttc 240

attaaaatga tgatagtgct tttttaaggt ataagccatc aactacaaat atcacaggay 300

agaggctatt agtaaatgag caatttcaat aaatcaaatg agcaattcac taaaaaatgc 360

attacaaatc tatttataaa gtttaaaagc aggcaaaact aaataataat tgtttagtaa 420

tacatacata ggtggtaaaa ctatttttaa taacaaagga atgattatca caaccttcag 480

tgtagatgtt acctctggag gggaggggca catgatgaag agggagaaca caggaacttt 540

tatgctgttt aaccaaggca agaggtgcat gggtattcat tttgttatac atttattgt 599

<210> SEQ ID NO 54
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 54

tacagaaaaa acgaagaggg aaaagattat cacagaaatg ctaatagata atttccctaa 60

gatggatcca gtcttcagac taaaagaact cattctgtat ccaggactta aatgtgtcct 120

ggaaaaaaat gttatatatc taaggataaa gagaagaccc aaataactgc caaggagaaa 180

atacagctca catgcaaagg aataagagtc aaagacgtta gctttctcat cagaacacag 240

aatgtggaaa gtcaatgaag aaaggtcgtc aaagttccca ggaaaaaatt attttcaacm 300

catatttcta taactaacct tataaccact gaaaagaaca tcataaaaat gtttttttaac 360

atgcaaggac tcagaagttt actcaaatgc accatttctt agaaataaaa atgtatctca 420

agaaaatagg caagtattcc atcaaaacaa aggaagaaag cataatggcc tcagaaacag 480

tgatacccaa actaagagag gaatgaagca aaattccagg atgacatcca cactgctgtt 540

ctagagagtg ctagtaaaga ttggggccag agaacagaat gttttgcatg ggaagttca 599

<210> SEQ ID NO 55
<211> LENGTH: 599
<212> TYPE: DNA

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 55

aaaacaattt tgaaaaacaa caaagttgta ggatttacac tccctgattt caagatttac 60

tataaagcta tagcggtttt tacaatgtga tctttggcca agaatagaga agtaaatcaa 120

tggaacaaga tgaggtccag ccataagccc acctatacat ggtcaattgg ttttcaacaa 180

aaatactaag gcaatttaag aaagaaagat aatgttaata aatggtctgg aacaactgaa 240

tctccataag aaaaaaagaa gaatcttgac cactacctct taccatgcta aaaaaaaaar 300

gggggaggcg ggtgaatatc ttcatgagtg tggagtaaag atttgtttac actaggccaa 360

aatatgtgtg tgtgtgtata tatatatata aactttaata aattttactt catcaaaatt 420

aaaaactata actattcaaa aacaccatta tgaaaatgaa aaggtgatcc acagattggg 480

aggtaaatct ttccaaaaca tgtatctgac tagtattaaa gatatacaaa gagttctgta 540

tcaatcaggg cttgattaat gaaacagaac cactaagagt cccatacata tgtgtatgt 599

<210> SEQ ID NO 56
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 56

tctcttccta ttcagatgcc ctttttctct ctctctcttg cctggttgtg ctggctagga 60

cttccaattc tatattgaat aggagtggtg agaggagtca tccttgtctt gtgcttgttt 120

tcaaggggaa tgattccagc tttccccagc taattaattt ttttttctc agagattagg 180

tctaattatg tttcccaggc tggtctccaa ctcctggcct caagtgatcc tcctaacttg 240

gccttccaaa gtgctgggat tacaggtgtg agccactgtg ccctgctcaa atccatgaas 300

ttttgagagt ggagatgtac gtgactttct tatcagaaag ctaagacctg ttccatgtct 360

gagtctcact gctcataatt tctttgagtc atttgctgac atgatcctgc tcacacccag 420

agaaagctgg gtggcactgt ggaaggaatc atggagtgag agcccagaaa cataaggtgt 480

agactgtctg ggccctgtga gcaactggtg atagcccaga tgctggactt ccctgcttta 540

ttttatctgt aaaacaatct taatagtatc tacttgtgtt aacttccaat ggctgatgt 599

<210> SEQ ID NO 57
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 57

caatattgtt aaaatagcca taccgcccca agcaatttat aaattgaatg ctattcctat 60

taaactacca acgacattct tcacagaacc agagaaaacg atcttaaaat tcatatgaaa 120

ccaaaaaaga gcccaaatag ccaaggcatt cctcaacaaa aaggacaaag ctggaggcat 180

cacactatct gacttcaaac tactgtaccg ggctacagtc acaaaagcag cacgatactg 240

gtacaaaaac agacacatag acaaatggaa cagaatagag aacccagaaa taagaccatr 300

caccaactat tatctgatct ttgacaaatc ttacaaaaac aagcaatggg gaaaggattc 360

cctactcaat aaatggtgtt gggaaaactg gctagccata ggcagaggtt gaaactggtc 420

cccttcctaa cacctatatg aaaattaact caagatgaat taaagactta aatgtaaaac 480

ccaaaagtat aaaaactctg gaagataacc taggcaataa cattcaggat ataggcacag 540

agaaagattt catgtcaaag atgccaaaac aattgcaaca aaaacaaaaa ttgacacat 599

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<210> SEQ ID NO 58
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 58

caatgtgaga gtacacttat cttgctttgc ccaaagatgt gtcagcaaca taaccttcag 60

actaaaacca aaaatttcaa tttagagtat ttatcccagg acctaaaaga cactaaggcc 120

taccacacac atcaatcatt ttaaacaatt ttataggagg actatgtgaa tttatgttat 180

tgagcctctt gtggcttggt accaggagtc tccttttgta agaaatcaaa taaatgaccc 240

tgaccttctt caagaattga aaagtggttc agagaagtac tttgttttat ccgggtagcr 300

ggttaagtat caaagtatca tcccttagag aaactgattt aacacattaa attatgaagc 360

aatctagagt gtccccaggg ctgctgctta ttattgacaa cataagtagg tggtctagaa 420

gtaaatgaat atatgggaag agcacagcag ctacacgttt cccaactcca tgggggcatc 480

attcacataa aagacatgtg agcagtgacc tctagaattg tacattaccc tcagtccctg 540

agggtttgag atttttgag actgtatact cttcagcctg tcacactcat aaactgcct 599

<210> SEQ ID NO 59
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 59

tgcctacctg tttaatacag tgacacagaa actcccattc gtctctaaat atttccacca 60

ccaacctgct aaaagagttt aaaaatccaa tctctagagt catcctttgt attaataatt 120

attactgaaa tgattatttt aaagtgtaat ggatacttgg aagaggcaat acaatctata 180

taatactgag cagaaaataa ttaaatacta acatctcttc cattcttctt agagcttctg 240

taagatatgc agaagaagtc aatgatgtca gagatgttat cttcttgcta caaattgagk 300

gatcacatac tcaacgtata cactaagcag gaaggaaccc attccaccag gaagaactta 360

gtcaatcttc ctactgatat agcccatgca ggtcctaagt gtagcaaaca atgcaaatca 420

tggtagagaa cagaaaatgc aaccagtagt gagagaaaga agaatcaaga caaacagaac 480

ttgggctaca gagaaaacac aatggccaag gaatccataa aacctatttc ttttacaggg 540

aatttggctg cctgaactcc tcagactata taaaaaagga gcaaaccctt ttttaagca 599

<210> SEQ ID NO 60
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 60

cactccagcc tgggtgacag agcaagactc tgtcttttt ttttctttat tactatactt 60

taagttttag ggtacatgtg cacaacatgc aggtttgtta catatgtata catgtgccat 120

gttggtgtgc tgcacccatt aacttgtcgt ttagcattag gtatatctcc taatgctatc 180

cctccccct ccccccaccc tacaacagtc cccgctgtgt gatgttcccc ttcctgtgtc 240

catgtgttct cattgttcaa ttccttaaaa aaagaaagaa agaaagaaag aaagccttay 300

cttatcttat gggaaatcaa tggataacat gggtgaaaat actacaagaa atggctgaaa 360

taaataaaaa tgattgcctc tgggaggact gggaatttgg aggggcaaga caaaggacag 420

cagtttttca ttattatgct attttatatt tcacatttat gaaatacttt gagatacaag 480

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tgagaataaa tgaaacagtc aaactctgta tgttcaagaa gtatttgtgc cctttactct 540

gcttgaaaaa tctaaaattt tgatttagta aaaattgagg atgaatatat tctacaaat 599

<210> SEQ ID NO 61
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 61

gctaaatttc cttaactaca aaaaggtaaa atacagtctt acatcaggca aatgaaaaac 60

aagcagagga aacactatac aaagggaagc actataaaga ccatgcaagt atcacagaaa 120

ttagcacttt ataactttat aaaacatgat ctctccttta agtgtctaaa ttgtgactaa 180

ataatttaat acttacctga aaattatatg tttaatctgt gcaatcattt tttggcatac 240

aactttctgg actgtttttg ttttttcatt tgattagttg gctgggctgt tgttttattk 300

tgtgtgtgca atgaaaaatc tcatgtattt tagtgagttc atctgtacgc caagtactcc 360

aaccatctct caacttttca aacaaatccc caatggcctc cctgagttaa atcagcagaa 420

caataatatt tcatggctca ttagtgcatg caatcaagca acagatcctg atccagtagt 480

ggaaagggag aagcaatagt tggtttcaat tttgttaata ccacaatatg cccataggcc 540

tcagccaaaa ggtgtaaatt aaggattgaa cataaccacg aagcaattgg ctgacaaca 599

<210> SEQ ID NO 62
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 62

tgactaaata atttaatact tacctgaaaa ttatatgttt aatctgtgca atcatttttt 60

ggcatacaac tttctggact gtttttgttt tttcatttga ttagttggct gggctgttgt 120

tttattgtgt gtgtgcaatg aaaaatctca tgtattttag tgagttcatc tgtacgccaa 180

gtactccaac catctctcaa cttttcaaac aaatccccaa tggcctccct gagttaaatc 240

agcagaacaa taatatttca tggctcatta gtgcatgcaa tcaagcaaca gatcctgatm 300

cagtagtgga aagggagaag caatagttgg tttcaatttt gttaatacca caatatgccc 360

ataggcctca gccaaaaggt gtaaattaag gattgaacat aaccacgaag caattggctg 420

acaacaaaaa agggggggaaa aagactttta acagaaagag ctactgcaac ttaaattgtt 480

ctcacatttt aaatgtgtta acaatatcta tttttatttg taagccaact ttgtgttgca 540

actctgctga gtttcatctt ttaagcctct tttgcctctc tgagccagtt ttatcttcg 599

<210> SEQ ID NO 63
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 63

atccccaatg gcctccctga gttaaatcag cagaacaata atatttcatg gctcattagt 60

gcatgcaatc aagcaacaga tcctgatcca gtagtggaaa gggagaagca atagttggtt 120

tcaattttgt taataccaca atatgcccat aggcctcagc caaaaggtgt aaattaagga 180

ttgaacataa ccacgaagca attggctgac aacaaaaaag gggggaaaaa gacttttaac 240

agaaagagct actgcaactt aaattgttct cacattttaa atgtgttaac aatatctaty 300

tttatttgta agccaacttt gtgttgcaac tctgctgagt ttcatctttt aagcctcttt 360

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tgcctctctg agccagtttt atcttcgtat ttgaggcttt acattcaggt gacttctttc 420

attgcatttc aagggttctc taacccaaaa aaaagatgga agcagcacac gacaatcctt 480

tggggtgagt aaagaaaaat attagaattt ctatttccat tttctctaaa tataatatga 540

gtctacattt gatatatgga ttttcacagg cattcttgtt cagtaactat atcagagga 599

<210> SEQ ID NO 64
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 64

tggaattaca ggcatgagcc aacatacctg gccaatctct tcttattacg agtaactgtt 60

agccaagacc atcacttatg gccaaagtta ccacaataat tcagttaaca gctgcacaga 120

actgacaaga agaatgcatt gtgaaggcaa atcacagcaa aagcacacac agttgagaag 180

agctttgagt gggaggtagc ttttgcttga cattttgtt ccagagatct agaagcttat 240

ctttctttta ctggcctccc tccaaggttc cagccccagt gttagcaaca aaccagactr 300

tttgccattg ttcaatcaca gaatgttctt tcaaatctcc aaactgttct tgctttctgt 360

gcctgaaaac agctcctcat cctccttcaa ggcaaagttc ccaaatacgg catttgaatt 420

taattacaat ctattgatta tattggcttt ttcctttggc aaaacttagt gatcctactg 480

aaatagggat tatagtgtag caaagtaatt aggagttaaa tagaaaacct tcttctaagg 540

actgatgttc ccagaaagga ctcttgtgat ctcagtacaa atggtcccta aatgaatgc 599

<210> SEQ ID NO 65
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 65

tatacttcta tgtgtacaaa atcaggaaga acctcttatt ttccctagag cagatcttgg 60

ggatgttgca taccagttca catttattga gcacttgtag gtgctatacc aagtgttgaa 120

tggatactct ctcatttaat cctctcaaga gtcctcagac acaaccatta ttatcacact 180

tctgaagttg tagaaacagg catggagaac gaactcactt gtgcaaagtt acacagcatc 240

agtcaggatt cagattgttt tctgttgact ctgaagttca taccattaac tgctatactm 300

caaaaggtgc ttgcctaaag atggtcctat acttttgact ttgtagtctc tgaagcttaa 360

gtacctctgg gttttgcagc agctatggac atagaagcat gtatggtaat aataatgata 420

aagctatcaa ttgtaataat tataatggtt aataatataa atgatagcat ttataacaat 480

ataattagat aatatagtaa ttaatatttt tataatgtgt tatatgttag taatattata 540

aaatagctat cttcaataac ccttacaata tgctagacaa tgttctgtgt gttaaacca 599

<210> SEQ ID NO 66
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 66

caaagataga taaaattaga tttaacaata ggaaacatat tttcaagaag tatagttcag 60

ttttactctt gggaaacata tttttataga gctaaaagta aataatgtcc taatctgaga 120

ggcctgaaat aacactgctg aaatttacat gctttgttga atgcgacttt tagaaatgtt 180

tactcccaag aagtctaggt tcaagatgta tataaaatga tattgataat tcacatgtat 240

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taattgttta ttatttgcta agcattgtgc tagatgcctt cctcttacag tcttatgagr 300

taggcacagt atttgcatcc ttgttttaaa gatgagaaaa ctgaagctta gggatgttaa 360

gtgacatgcc atactcatac ctcggcagga tttgagtgaa agtctgactc tcaaatttaa 420

gcttttaatt agtatcctat acagatttta taggacaaat ttgttaagtc agagatacaa 480

gccctctgtt gttgtcacct tttaacaatc tttcttcctt cagagaactc ccttaccctt 540

caagtacaca gcttcttcct gatttctagg gatccttctt tattgagaaa tttcatgct 599

<210> SEQ ID NO 67
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 67

cacctaagtt tccttttttt cattcaacaa gagctgcaat tacagtctga gaagtcagct 60

tttccaagtt tctgctgtgg taaaaatcaa cccccaaatc ctgttgtttt acaaaaaagg 120

tttatttcca gcctatgttc catattgact gcaggtgggc tgtgactctg ttccacgttt 180

tcttcattcc aggatccagg ctgaaggaac attctctatg acacaccatt cttgtgccac 240

agggaaaaaa gcaatggtga aatgactgat ggcaagtaaa gtttatggtt agacaacatr 300

taagtcactc atgttcccat tagtcaaaga aaagcacatg gccaaccctg gggctgggaa 360

gtacaatcct cctatgggga actcagtgaa taattgggga aaataataac aacctagcac 420

atggaccctg gggaagcaag ttctttaata cacatctaca atcatgtgaa gaaccatgac 480

atttaaagaa tataacttag aaagtaacta ttttgggaac tactgcttaa gaatgtttgt 540

ttaaggtctc ttaagtcacc agataatctg aagaagtttc tggtcagcag gaaaaggta 599

<210> SEQ ID NO 68
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 68

caagcctagg ggaggtgtca catcaagtag tatctgaaaa attgcaaaag tgaatcagta 60

ttttttttt aaggtggagt ctcactctct gttgccaggc tggagtgcag tggtgcgatc 120

ttggctcact gcaacctccg actccctggt tcaagcaatt ctcccgcctc agcctcccga 180

gtagctggga ttacaggcat gcaccaccat gcccagctaa ttttttgtat ttttagtaga 240

gacggggttc accatgttgg ccaggatggt ctcgatcagt tataatgagc ttttttttcay 300

atacctgttg gccacacgtg tcttcttttc aaaagtgtct gttcatgttc tttgcccact 360

ttttaatggg gttgtttttc tcttgtaaat tggtttaagt tccttataga tgttggatat 420

tagacctttg tcagatgcat agtgtgcaaa tactttctcc cagaatgtag gctatctgtt 480

tattccattg ataatttctt ttgctgtgca gatgctctta agtttaatta ggtcccactt 540

gtcaattttt gcttttgctg tactttattt tggtgtcttt gtcattaaat ctgcccatt 599

<210> SEQ ID NO 69
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 69

gtcactattc aagagctagg agagagagat gagatcaatg atgttcaaca gaaatctgat 60

ccaagccaca tacttgattt aaaattttct aatagtcaca ttaaaaacgg taaagaaaaa 120

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accaggtaaa atgaattttt tttaaatttt attattatta tactttaagt tgtagggtac 180

atgtgtgcaa tgtgtaggtt tgttacatat gtatacatgt gccagaattt taatagtata 240

ttatttaacc taagatttct aaaatattat ttcaacatgt aataaatatt atttgtatts 300

ttttttggtg ctgattcgga aatcagtatg tgttttaaac tgacagcaca tctcaattgg 360

actagcctaa tttcaagtgc tcaatagtaa catttatata gtggctacca tattggacag 420

ttcaacaata gataattcag aaaagagcta ttactacagc tgaaagaaac aagaaatgtc 480

aaagtcacgt gccaccaata ctgggttcgc cacattttct ttgtacatga aggatagctt 540

atttttattg ttctggggaa acagatgagg atcacatcac caggatgctc atccaggag 599

<210> SEQ ID NO 70
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 70

ctggctcctt gcttctagcc ctcctaggct cctagatcaa ttgtattccc attatctgag 60

gtagcagaac atattccata taaatgctaa accatcacag ctgtagatca tgtgcctgcc 120

cttttgaacc ccacattctc accaactgtt tctttgttag attaccaata aatagcatgg 180

gctcccagag ttcagggcct ttgcagcctc cacgatcgtg atggcccct ggtcccactt 240

tacttctcaa actgtctttt tctcaatcct ttgactccac tagactttat cgcccccacr 300

acgtggtgtt gggtctgatc accccaacat tcctggctgc ccaatgtgga gcaacaaaga 360

cctggtgaag aaatgctaga gcgtgtgaaa gcggacgatg cattgtcaaa ggatacccaa 420

gtacgtctaa aagaagctcg gtgggaaagc tgagcactcc ggaagaacca gggtaacaat 480

gggacaaagt gaaagcagac attctgcttg tttaaatttc tgaaggcatt tactacaaag 540

agatgaagtg aaagttagca ctcagaattt gttatcactc tttattgcag taaagcagt 599

<210> SEQ ID NO 71
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 71

tacatgttac aggggaaaaa tatccttctt tcagttctgt ctgacaagga cctaaagaat 60

cctattgatt ttattgctcg gctccaggag gctgtgtata aaaccataac tgataaaata 120

gctcaagatt tgtaatgcag cttcttgcat acaataatgc taatgcagac tgtcaaactg 180

ctattagacc cctgagaggg aaggctcatt tagctggata tactaaggct tgcgatggca 240

ttggaggtaa cttacataag gctactcttt tagctcaggc tatggctgga ttaagagtcr 300

gaaataatat gccccatttc tcaggctctt gctttaattg tgggcaattt ggacacagaa 360

aaaaggaatg tagaaaagga aatcaaaagg caagagctac catcaaacaa cagaaaagtc 420

ccagtgtatg tccccgttgt gaaaaaagcc atcactgggc aagtcaatgt cattctaaaa 480

gtagcaaaga tggacaacct ctctcaggaa acaggaatag gggcccgcct tgagcccctc 540

aacaaaccaa ggcatacctg gcacagccag tgcccttaca aatgtacaat tgtcccctg 599

<210> SEQ ID NO 72
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 72

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aaaaaagcca tcactgggca agtcaatgtc attctaaaag tagcaaagat ggacaacctc 60

tctcaggaaa caggaatagg ggcccgcctt gagcccctca acaaaccaag gcatacctgg 120

cacagccagt gcccttacaa atgtacaatt gtcccctgcc acagcaggca gtgttgtcgt 180

agacctctgc agcacaattc ccctctcctt acttcctggg gagccacacc aaaaaaggtc 240

cctatgggag ttaggggacc cttaccagca ggaacagttg gtctattact tggaaagtck 300

agttaaattt gaaaggtgtc actgtgcata tgggaataat tgattctgat tataccggag 360

aaattcaatt agttactagt tcctcaactc cgagatctgc ttccccagga gaaagaattg 420

ctcagttgtt gctgttacct tacataaaac taggaagcag cacagtgaag agaacaggag 480

gctttggtag tactaatcca acaggaaagg ctgtatactg ggttaatcaa atgtctgaca 540

aaagacctat ttgcacagta actattcagg gaaaagatta tgaaggacta ctagatact 599

<210> SEQ ID NO 73
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 73

gttagctttg acactattaa aatttggaat taaatacttt tgggaggtta aaatatctgt 60

gggcaaagct acctctaatc cactgctttc aaggagagac atcaagaaga agcagtcttt 120

atcaaagtga gagtttcaca gcttaaatct gaaaagaact gtcaaacatt tcttagtctc 180

ttggatacga tgtaaattag ttaagatata attacaacta atacttgtta ctattactac 240

catagcttca tttataaaat attacttctc cactaattaa atgaagcatt cagtgcttcs 300

cataaccaat taaaatgtta agtagttaca ttatgcagct agatatgtga aaaccaagaa 360

taataagcca gataatacaa aagaaaaaca gtgatgtgaa atgagttaca gcgaaaatga 420

gcaaagtgaa aacacattta aaccataaac ttttctgaaa atttgaggtg tccaagagga 480

cagtcaagca tgtacacaga atcaggtggt atgaaatcta acagcaaaat atagggtagc 540

ccagtctaac aacaaaatga tatagtggat tggctgattc aggtttattt tcactcaga 599

<210> SEQ ID NO 74
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 74

cagtctttat caaagtgaga gtttcacagc ttaaatctga aaagaactgt caaacatttc 60

ttagtctctt ggatacgatg taaattagtt aagatataat tacaactaat acttgttact 120

attactacca tagcttcatt tataaaatat tacttctcca ctaattaaat gaagcattca 180

gtgcttccca taaccaatta aaatgttaag tagttacatt atgcagctag atatgtgaaa 240

accaagaata ataagccaga taatacaaaa gaaaaacagt gatgtgaaat gagttacagy 300

gaaaatgagc aaagtgaaaa cacatttaaa ccataaactt ttctgaaaat ttgaggtgtc 360

caagaggaca gtcaagcatg tacacagaat caggtggtat gaaatctaac agcaaaatat 420

agggtagccc agtctaacaa caaaatgata tagtggattg gctgattcag gtttattttc 480

actcagatat caagatacac ttgagagcac ttttcctgga ctaaattgta actttcaagg 540

tgaagatgta atcatgagac tagaaccctg tgtaaggggg cagcagagac aagtaaaca 599

<210> SEQ ID NO 75
<211> LENGTH: 599
<212> TYPE: DNA

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 75

cacagaatca ggtggtatga aatctaacag caaaatatag ggtagcccag tctaacaaca 60

aaatgatata gtggattggc tgattcaggt ttattttcac tcagatatca agatacactt 120

gagagcactt ttcctggact aaattgtaac tttcaaggtg aagatgtaat catgagacta 180

gaaccctgtg taaggggggca gcagagacaa gtaaacaaag ctgactggca aaaatcccca 240

tggtccacac agcatcctat tctacctgta tcatttaagg tgccagaaga taaacaaccr 300

caacctatta agaaagcaag aaacaaacct ggaaataaaa taaaagccta gacggaaagc 360

tatacccagt gtctgggtta tttgtgagat aaaataggat aatacctcac ttcatttctg 420

gaaagtctaa atccaattac ttaaaaaaaa aaactcacta tagagaacat taacaaatat 480

ttatctcttt ctacttttcc caatcacttt tccttaaccc tttgctatct ggttaacagt 540

aaaacatttc tttgaatggt cactaaaaat ctgctaaata ttacatgcaa taggcatgt 599

<210> SEQ ID NO 76
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 76

agagcacttt tcctggacta aattgtaact ttcaaggtga agatgtaatc atgagactag 60

aaccctgtgt aaggggggcag cagagacaag taaacaaagc tgactggcaa aaatccccat 120

ggtccacaca gcatcctatt ctacctgtat catttaaggt gccagaagat aaacaaccgc 180

aacctattaa gaaagcaaga aacaaacctg gaaataaaat aaaagcctag acggaaagct 240

atacccagtg tctgggttat ttgtgagata aaataggata atacctcact tcatttctgk 300

aaagtctaaa tccaattact taaaaaaaaa aactcactat agagaacatt aacaaatatt 360

tatctctttc tacttttccc aatcactttt ccttaaccct ttgctatctg gttaacagta 420

aaacatttct ttgaatggtc actaaaaatc tgctaaatat tacatgcaat aggcatgtct 480

tcatcttcaa gtttttgacc tgtaccatga cattatggat cacctctttt tgacaattat 540

acaaactttg gttccacaac attgtactat cttaatcttt cccttacccc tttgagcct 599

<210> SEQ ID NO 77
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 77

ccacacagca tcctattcta cctgtatcat ttaaggtgcc agaagataaa caaccgcaac 60

ctattaagaa agcaagaaac aaacctggaa ataaaataaa agcctagacg gaaagctata 120

cccagtgtct gggttatttg tgagataaaa taggataata cctcacttca tttctggaaa 180

gtctaaatcc aattacttaa aaaaaaaaac tcactataga gaacattaac aaatatttat 240

ctctttctac ttttcccaat cacttttcct taaccctttg ctatctggtt aacagtaaar 300

catttctttg aatggtcact aaaaatctgc taaatattac atgcaatagg catgtcttca 360

tcttcaagtt tttgacctgt accatgacat tatggatcac ctctttttga caattataca 420

aactttggtt ccacaacatt gtactatctt aatctttccc ttacccctttt gagccttttt 480

tctgttcctt ttggcttctt catttaccaa tatattttcc ataagtattt aattataaag 540

tgtaacaaag tctaaagtga ttttagtaca tctgacatct ttttgaacaa ggcaaggac 599

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<210> SEQ ID NO 78
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 78

gcaggtggtg gtgcgagtga gcagcaccaa ggaggcggca gccgaggcca aaaagagcgt 60

ttgtcgccgt ctagattaca tcacgcagag cctccagcag cagggcgtgc aggtgagatc 120

tccgcggggg aggaaataag agccggaaga cacaaaaggg ttggcagatg gtcgggcccc 180

acaggccccc ctagcgggaa gggagatgtg gagggtctgg agcgtttagg acgcgtttgt 240

tgcaaaggta ctccgggacg ccaggacctg gcagagtgaa tatttgaccc attcttctcy 300

tagacgaagg taattattgg cctcaggcaa attaaaaata aaagaatgca aattgggtag 360

gtttttatct ggggatattt gcttcagtga ttttgttttt aaatttaaag tgatgaaatg 420

ttaaaacttg aaatgttagt tgtaaatact tgcccacgtg gagtgctgga cactaaatat 480

tttgttttgt tttgttttta ttccgcacca tggaattggc aagtgaagag cacgacctgc 540

ttccttccga tcatgtaaaa ctttgcatgg aatggttctt gagtatgttc cgcaaacag 599

<210> SEQ ID NO 79
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 79

aatagtcttt gtttcctgca accatattta ttttaaaaaa tcctacagtt cactctaaat 60

agacaaccta aacttatttt tgtggccaga gaaatgccag accaattagc ttagatatgg 120

atttctgtcc atcttttaac ctaatcctat agcaaatcag atgtgatcat cctaagtagt 180

ttaaacctat tacggcttac cctgaatcac atagttactg ctcagaggta gtaggggaag 240

agtgtatgac atgaggattc tgtatttctt gttttaccta ctgctttgaa atgttactgk 300

ttattgctat ttgtaatctt cagatgttct tgaattagtt acagaattaa ttagttcatt 360

tgatccttgt tacggtcctg tgccagtact atcctgttta aattattatc ttcataaagc 420

atttgtaggg caagttctcc cctcattact cttctgaaaa aaattccctg tctgcaagga 480

acagagggac attttaagtg acaacatgaa attatagtca gaaattccag agggtggaaa 540

atttctatac aaaaaatttc tatttatatt ttgcattcag tttacaaatt aatttcagg 599

<210> SEQ ID NO 80
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 80

cactatagaa tgggagaaaa tatttgcaaa ctatgcatct gacaaaggtc taatgtccag 60

aatcctataa ggaataagca ggaaaaaaaa caatctcgtg aaaaagtggg caaaggaaat 120

gagtagacac ttctcaaaag aaaccataca agcagccagc aaacacatgg aaaagtgctc 180

agcatcacca gtcattggaa agatgcaaat caaaaccaca gtgaaatacc gtctcacact 240

agtaagaatg gcttttatta aaaagtcaaa aaataacaga tattggcaag attgtagagm 300

aagaggagtg cttatactct tggtggaaat gtaaattagt tctgccactg tgaacagcag 360

tttggagatt tctcaaagaa ctagaaataa aattaccatt tgacctggca atctctttgc 420

cgggcctata cccaaaggta aataaatcgt tctaccaaaa agacacattc acttgtatgt 480

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ttattgcagc actattcaca atagcaaata catggaatca acccaggtgc ccatcaacaa 540

tggattagat aaagaaaatg tgatgcttat acacaatgaa atactgtgta gccataaaa 599

<210> SEQ ID NO 81
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 81

ctgccttttg tatttagaaa taaacagtag cttaatcaag aaaacttagc agagtaggct 60

gatatatttc aatatttttc agttttgtgc cccttatagc aggctttctc aatcttggca 120

gtattaacat tatggattgg ataactcgtt gttgttgggg gctgtcctgt gcattgtagg 180

atatttaaca gcattcctgg cccctaccca tggggtgacc agcatgtcct cctttacctg 240

aaactgttca agttttaaaa ctggcaggtc catgtctgag gaacctcctc agtttgaggw 300

tcacagggac acttgatcat cttgtgtatc cacttagtag tgtattcctc ttccccagct 360

gtgacaataa aaaatgtctc caggcattgg cagatgtccc ctagggcaaa atcatctggt 420

ggagaaccac tgccctatag ataaacaaaa aatctcatac tctgtgttgg aacccaccag 480

ccagactatc agaaacgtat ctatagtgaa acaaagttag gtttatttag catgatgcaa 540

caaagaataa tgcatcccaa aggaccttag gagtgtttca gaaacaggta ttcaggagg 599

<210> SEQ ID NO 82
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 82

agaggattac agttaggcta ggtgtgcctt tagtaaaggc acagcaatca agcagaaaaa 60

gaatgttaat tatttcttgt ggttgcaggt ctgttagttt ctgttagaaa ctttggctct 120

gttaaaaact ttcttagatt ctatgtcctc tggaaacatt gtttatgttc tgcttagacc 180

ttctccatct gattgtcaac aggcaatttt tatttctcca ttccctgtaa tattatttag 240

aatttcaaaa tatatcagat attttactat atagagaagc aagataactg tcttcttatr 300

tgggttgttt tcagactgca cacacttccc tttaaaaact actgggctgg cataggttcc 360

aagatggcca aataggaaca gctccagtct acagctccca gcgtgagcga tgcagaagac 420

gggtgatttc tgcatttcca actgaggtac tgggttcatc tcactagggc ttgtcagaca 480

gtgggtgcgg gacagtgggt gcagcccatg gagcgtgagc cgaagcaggg cgaggcatca 540

ccttacccgg gaagtgcaag gggtcgggga attccctttc ctagccaagg gaacccgtg 599

<210> SEQ ID NO 83
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 83

gaagcaattc gataaagaaa ggagtctttt caacaaatgt tgctgcaaca gtcaaatgtc 60

tgtatgcaaa aaaatgaacc tccacactca cctcacacct tatacaaaac tttgttcaaa 120

attggtcaat attgagcatg tagcatctgt tgcctgttac caggatagaa gtccaagcac 180

ttctgcccac tgcattttgg tatgagagtc accaagaaaa cacaatgcag tcaagcactg 240

gatggaacaa accttactta tgtagagaaa agacaagagt gacatcagag tcagtagtas 300

atgtcagtcc cccatggcca gcaactgctt cccagcagct aatgcagggg cagttgacct 360

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acatgcacat ctcttgtgct gcaacagaag gactcagtcc ccttcctgca gggtacagat 420

atagtagtga ggttggtcag gtgtcatatg acatacaacc tttaagtaga agcaaaaagt 480

acatattgag tctgaaatgg ggaaggtatt cccatacaag gaaacaagcc cagcacaagc 540

tctgaaagat actttatctc ttagtaagca agtgttccag ggccacagcc cattcctgg 599

<210> SEQ ID NO 84
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 84

tttgagcttt tcgaattttg gattttcaca tttaggatgc tcaacctgtg ttaccaaaaa 60

gcacagtcca tgaaacaaac aaaaagataa attgtatttt atgacaatta aaaactcact 120

ttgtgaaaaa cattgttaag aaaatgaaaa gtcaatctat agactgggag aaaatatttg 180

taaattacat agctgataaa ggacttgtat ctgttaagaa aatgaaaagt cagtctatag 240

actgggagaa aatatttgta aattacatag ctgatgaagg acttgtatca agaacatatr 300

tagacctcaa ttcagcagta acaaacagct caataaaaat gcacaaaaga tcttaacaga 360

cacttcgcca aggaacttat acagatggca aataggcaca tgaaaagata ctcaacatta 420

cttgtcaata gggaaatgga aaataaaacc acaatgaaat actgctatgt acctattaga 480

atggcttaaa tacagtaaca ctgataccaa atgctgggaa ggatacagag caacaggaat 540

tctcgttcat tgctggtgag attgcaaaat tatatggcca ctttggaagg tagtcttat 599

<210> SEQ ID NO 85
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 85

ttggaagcat gtcactaagt gcagcccaca ctcactcaat aaatactact ttatttcttt 60

tgttgctcaa ttgttctagc tttggccatt gggacttctt tcaggttggc tcctttatct 120

gtttgacata ccccttcct ttacttttg agcactttct tactttctgt tgcaagatat 180

tataggctta tgcagtttcc ttgccccagt cctagaataa gccctttctc caagaagcat 240

agtacctttt ctttgagatt tatgtagaac caagatctga atgctgagac tgctcactgy 300

tattggggtg tcattccttc taggctctct cagtggacag agctaggtta catatatata 360

tgcatagaca tatatatacg cacacagata ctaacttaca tgtaaaattt tctgtatttt 420

tccacctgta caatatacaa aggtaaacat gagttcacac tgatgttttc aactctaatc 480

ctgaatcaca gaattcattt taaccttcca tttttatctg taacttccct ctctgatagt 540

gagaaacctg gctcccacca tccactatcc acttatttat ttgtttaacc ccagtatat 599

<210> SEQ ID NO 86
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 86

tttaccgtat tgtgataaat attgtttaaa aatgaaaacc attcaacctt tatacaaatt 60

gaaaagaata aaactatttt caaattataa aaggagtgac atttatgaaa ttttaagcaa 120

aatcaatttc tgaattcatt ttatgtcact tttaggaaag ttttaaaaca tcaggcaaag 180

ttctttttgc atattttatg tttttctgat tttaattagt gtaggtttct aatttatgtt 240

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ttagagtaat tgcatcaaat atttagtaat catactcttg gacttttct gtttcaggcr 300

gaaaatataa ctgtgacaaa ggattttagg agagtggaaa atgcttatca catggaagca 360

gaggtatgta cttaacaaat aattggaagc agcatgattt tgtggagaca gtcattttta 420

ttcttgaact gaaatgaatg gtgaaaaatg cttctcatga tattaataga agattatttt 480

tctcaaaatc atcttggtgt tatatatcta tttcggcttt taaataaact tgagatttaa 540

aagaaagttt aaaatggaat aaaaacagca agtgggaaat agcagttaat tgccactaa 599

<210> SEQ ID NO 87
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 87

aaatgcaaga tttgaatttc catattcagt ggacccagtg ggtgcccagc gcaatgaaca 60

acaacaacaa caaactcatc aaagcatatt ggaaatgtta gaaccccagg aataaaagga 120

ctccaaaagt tctagagaaa gaaaaatagt tcacaaacca agggtcagaa atctgaacag 180

caattggacc tctcagtgtc aacactggaa gctagaaact gaaaagcaag acagcaacat 240

cttccaattc tgagagaaaa caatgtctaa tctagaaatc cttacctggc caaaaaacar 300

tgaaggagac ggtaatacaa ggacaagcag acagggctga ccagaagtgt cacactgttc 360

tttatttggc caggatctga tggattaatg ccctctgaaa gatgttaaaa atgtgaaaca 420

tcactcctgc atacaaggtc tcaaaacatt tccctaccat acgtgaggaa gcaaaccaag 480

aaagagaaaa acaggagttc ccaggtaatg gcaaaggaat gtccccagat tcaggggaca 540

ggaggactaa gggcttcagt aaaatgcctc caagaaaaaa ataaaggaac tcatagatt 599

<210> SEQ ID NO 88
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 88

ataaaattta aaatttagtt cctcagtcac actagccata tttcaagtac ttgaaggcca 60

caaatggctt gagactacct tgctgaacag accaaggtca aacactgaga taataatgat 120

tcttaaggcc atttgaaagt taacagcaag tatgtattac tgctatctac agtaagaatt 180

acattttatc tacaggcaat cataagccat gtctgttatg cagcataggc tttccattct 240

ctatacatct aggtcataga gtttttccat tgataaatct ggatgtttat ataccaacak 300

tactttctta caacatattc cagtatatag tgtccagctt cacccacttt ttaaagtggc 360

cctgaaacaa ttttattcat cttattggag tgttgctgta ggggaagagt agaagctaag 420

aagagtttga gttcaacacc attatatcca aatcctgacc ttactactgg aatgtaagct 480

ccttgaaagt ggagatcttg tctgtcttgt tcacagttgt gttcccagcc ccagaggtag 540

tctcagggcc aatatcaagt atgctctcaa atatttgctg ggaaaattta ctagctgga 599

<210> SEQ ID NO 89
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 89

atacatacat acatacatac atacatacat acatacataa aatgcccagt atcttacaag 60

actgtagttc acagtgggta attcaaatca gacactgctc ttcaagagag gtaatattaa 120

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tagaaatctt tcaagaagga ttgttttcta ctattaaaac aataaaactc ttataaacct 180

gtttatcaga aggatatttc tgtttcagca actcctggaa tccttcttca acatcccaac 240

caacaattac tcccagatag ccatgtcacc tgtgaattat catgaatccc acatcaaatr 300

aacaaatact gcctctggac tctgaatgta agttggttca ttataagagt gagaaaaaga 360

agactaagaa aaagcatact gtattctttg ctacataggg tttaaacttt attaggaggc 420

caggcatggt ggctcacatg tgtaatccca acacttcggg aggccgaggc aggtggatca 480

cttgagacca agagtttgaa accagcctgg acaacatggc aaaaccccgt ctctactaaa 540

aatacaaaaa aaaaaaaatt agctgggtgt ggtggcacac gcctgtaatc ccagctact 599

<210> SEQ ID NO 90
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 90

ccatttttca gaataagaca ctttttcagt gtctttcaaa aataaagatt ctgtctccta 60

tcctgctcct tttttcaaag aacaattttg ggcaaagagt aaaatacaga catatagttt 120

cagtgcttca tatggacatc agttttacgc tggtcacatt aattatgccc taattatttt 180

ttatcttccc cttcacaaga ctgtgaactc ctcaagagta gggctatgct tgaaacagtt 240

tttttcccaa ggtttgggta ataaaaggct aaggaggaaa aaagttggct gtgaggtaty 300

gtgctttatt ctcaaataag acagatactg tttatggcaa agttacctga acattggtac 360

acctggaagc agggatggga aatgcaggac acatattcaa actgtgtttg cacattttgc 420

agtccaataa gcatgctttt atttctccag agcttagctt tctcaaaaag tagtttgtgg 480

ctatgcaaca acatacattc tgttgtgtaa acaagcctct taaatcattt cagaacctat 540

gttcatttca agcttattgg atcagctata agtgtgtatc tttgcccttt acctcctat 599

<210> SEQ ID NO 91
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 91

aaatacaacg ctttagaagt gttttctcta aaagattaga cacttcattg accaatatta 60

attaatgata tttcatattg tttggtgata actctggaaa cataacactg caacagccac 120

ctaaataact atgagaatac atgaagctct gagttttgga cagatttcag ccctcagttg 180

atcactgtag ccctgatgac aggaaaagtt gaaacatcag caatgttcaa agagccatgc 240

aattactgct tctctatgtg tgaattagaa tattcagaaa gggacagaga catgcagttr 300

aagaaacagt aaattccttg aaaaatagtg tggcatgata gggcctataa tattacttcc 360

agaatatatg gaggtaatac tttgaatgct aagttttcag tctgctactt gttagaaatg 420

ttttttttga gattgaatct tgctctgttg cccaggctgg agtgcagtgg tgcgatctcg 480

gctcactgca acctccgcct cctgggttca agtgattctc ctgcctcagc ctctcgagta 540

gctgggacta caggcacatg ctaccatgcc tggctaatgt tttgtatttt tagtagaga 599

<210> SEQ ID NO 92
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 92

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acaaaaatac aggaaaaggg tggaagggaa acaatgaaaa agttcaggtg ggtcacaaac 60

atggacacaa ggagtctgaa aggcaggcct tgacatttgt ctgaataata ctaacgatga 120

cccttcggag tttcacggga gaggagggtt gccagactgt aatggagaga aactggactt 180

agttgctaat taggatgatg gtgcaaggtc catgacaggg gatgagggaa tgcctgctcg 240

gggaggggaa aaggggactg gacggagggc acggcaggat ggcctaggga ggacgggcgr 300

gggcctatca gttacaagag gaaggagaaa gaggatactg gttttcctct gcataaaaaa 360

cgcgatggat tctcaagaat ttattgaaag tctgtgtgtc caccatagtc caggatattt 420

tggaatattc aagggaaata caaatccaag aatttagctc aggaatcagc atcagaacag 480

aatccccgaa gagtaaacta ttcatggaaa acagtagact gataacattt gaaaaactga 540

tttcccatag aaacaatagt tactgtttga cgaattatac aacgtagacc taggtcgtg 599

<210> SEQ ID NO 93
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 93

ggtggcatgc acctgtagtc ccagctactc gggaggctga ggcaggagaa tcccttgaac 60

cctggaggct gaagttgtgg tgagctgaga tcacaccact gcactccagc ctgggcaaca 120

gagcaagact ctgtttcaaa aaaaaaaaag tacaagtcat tactggggcc gggcgcagtg 180

gctcacgcct gtaatcccaa cattttggga ggccgaggca ggtggatcac ttgaggtcag 240

gagttcaaaa ccagactggc caatgcggtg aaaccccatc tgtactaaaa atataaaaaw 300

tagctgcgca tagtggcaca cacctgtaat cccagctact tgggtggctg aggcacaata 360

atcacctgaa cccaggagcc agaggttgca gtgagccaag attacacact gtactccagc 420

ctaggtgata gagcgagact ctgtctcaaa aaaaaagtca ttgctgagaa gatgactgca 480

tctttaaaat acagtttaga ctaaaaagtg atgagagtga actaattaat ggctatttac 540

agtgaaacct ctacttttt cactccagga gtatttcaac tatttatatc aaaggaata 599

<210> SEQ ID NO 94
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 94

tcagcagaaa gctaacagca ggagatattg ggtgcctatt ttcagcattc ttaaagaaaa 60

gaaattctaa ccaagaattt catatcctgc caaactaagc ttcataagtg aaggagaaat 120

aaaatctttt ccagacaagc aagtgctagg ggaatttgtt accactaggt cagccttaca 180

agagatcctc acaggagttc taaacatgaa aatgaaagaa tgataactgc taccacaaaa 240

cacacttaag tacatagccc acaaccacac ctaagtacat aggccacaca gtagaaactw 300

caaagcagct agctaataac ttcatgatag gatcaaaacc tcacatatct tgcttgagcc 360

caggtatttg ttaccagcct agccaacata gagggatccc atctctataa aaaatacaaa 420

attagctggg tatggtggca cacaccggtg gtcccagcca cttgggaggc tgaggtagaa 480

ggattgcatg agcctagaag tttgaggctg cagtgagcca tgattatgcc actgcactcc 540

atcctgagtg acagagtaag accctgtctc aaaaaaaaat tatttttaaa atatcaata 599

<210> SEQ ID NO 95
<211> LENGTH: 599
<212> TYPE: DNA

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 95

gcacacacca agcctggcta atttttgtat ttttagtaga gacggggttt caccacgttg 60

gccaggctgg tcttgaactc ctgacctcag gtgatccacc caccttggac tcctaaagtg 120

ctgggattac aggcgtgagc cactgtgctt ggcctacaac atgtatttct taaataacaa 180

gacttgaaaa tcaaaattac tccttgatct gtgaggtgca gaacggatgt tgtgttagca 240

ggcatgaaag caacactaat caccttgtac attgccatca gagttcttgg gtgaccaggy 300

tgtcaatgag cagtagtgtt ttcaaaggta tctttttttat ttttttattt tttttctgga 360

aagcaggtct taacaatgga cttaaaatat tcagtaaacc atgctataaa cagatgggct 420

gtcatgcagg ctttgttgtt ccattgacag agcatggtag ggtagattta atataattct 480

taagggccct agaatttttg gaatggtaaa gaagcactgg cttcatctta acaccagctg 540

cattagcccc caatgagagc ctgtcctttg aagctaggca ttgacttctc tctagctat 599

<210> SEQ ID NO 96
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 96

ggagaaaaga acaaagactc aggaacttct aagtgtttag gatgactggg atacaaaaga 60

gagaaagaag gtaaaagaac ctggaatgtt aggcaagagc caagtaataa agagtcttgt 120

gtaacaggca aaaaatttaa aatgtttcca tatatgattt gaaggcaagg aagtgttttc 180

tctgtgtgta cgtacacaca tccacatgtg ctagagagaa ataaaaagat cgctttggct 240

gcaatatgag agagggactg gttaagaaag agttgagaac tgaggcagga agaccagttw 300

ggaaactagg aaaatagtcc aagcaagaaa ttatgtaggc cttgaaataa tgtcatggag 360

gtgagaatgg agaggagaga atagatttaa gagatgttat ggagggagaa acaacaaaaa 420

caaaaagctg ttgaacagat tcagttgctg aagagaaggc taggatgact ccctgatttt 480

aagtttacac gggtagatcc caatgccatt aacaaaaata agatttcagt agagaaatta 540

aattttgaga gaggtttctg aagacaacaa tgaagaaatg tcttagacac actttgaaa 599

<210> SEQ ID NO 97
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 97

ttcaaagctt tggaatgttt cacagaattc tctagtacta aaacatacaa acaaaattta 60

aaaattaaga gttattgaac ctaaagataa gaaaaaaggt taacctgaat tatttgaatt 120

agccaagaca acaaaacctg aaggatgctt aaagctttct taggaaagct actttctaat 180

aggaaaaagg cgtatccaac tagaaactct taatagtttc agccctttta gaagctgtcc 240

catcatttca aaatttcgaa ggcaagtctt ggcaaattgc tagctagtgt gggtactgtr 300

atttaaattc aggtagttta gatcagagtt gccattttta agcattagtc tataatgacc 360

taaacctcaa tttaattctt cttattaaaa actttttttt aaaataggaa attaataaag 420

aaggcaaaaa caacagtgtc tgctaggaat tactaaaact cagtatattg catttggcaa 480

agtaaaagct taaattaaga aaatcatcat atacatttca atttagaaag tgagtcttac 540

ttgttttccc tggtattgca gatgcattag cttttgtaat aaaagtcttt gcagctgaa 599

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<210> SEQ ID NO 98
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 98

gttttgtctg tatgagccat ttgaatttag agtcggactt ttctttaaga atctcaaaac 60

ttggaagatt tctgttctaa acacaaaaat acataattgt taaaatgctt cagtttacct 120

tttcatcaaa agattaggaa aaagggatgt aaaaaacaat aattaaattc taaatatttt 180

ttactggaaa aatatttaca ttacagtatt tactgaacaa aggtattttc ctccaaggaa 240

tggttgaaca ctttttttt tccctcacag atttacagca tgagtttgcg cctgtctgcw 300

ttctttgaag aacacattag ttcagtttta tcagattata aatctgctct tcgttttcat 360

aaaagaaata ccataaccaa aaggaggaag aaaagaaaca gaagcagctc tgtttccagt 420

agtgctgcat caaggtattt aatttctttt aaataccact agctgatcta taactttcat 480

ctaaatgata gaacttggtg ttttttaata cttcctttac tattccctat attgcagaat 540

gataatttga catgcaagtt cctatgatgt ggaggatttt taatctttta actaaagct 599

<210> SEQ ID NO 99
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 99

gacaataagt tttgtctgta tgagccattt gaatttagag tcggactttt ctttaagaat 60

ctcaaaactt ggaagatttc tgttctaaac acaaaaatac ataattgtta aaatgcttca 120

gtttaccttt tcatcaaaag attaggaaaa agggatgtaa aaaacaataa ttaaattcta 180

aatatttttt actggaaaaa tatttacatt acagtattta ctgaacaaag gtattttcct 240

ccaaggaatg gttgaacact ttttttttc cctcacagat ttacagcatg agtttgcgcy 300

tgtctgcttt ctttgaagaa cacattagtt cagttttatc agattataaa tctgctcttc 360

gttttcataa aagaaatacc ataaccaaaa ggaggaagaa aagaaacaga agcagctctg 420

tttccagtag tgctgcatca aggtatttaa tttcttttaa ataccactag ctgatctata 480

actttcatct aaatgataga acttggtgtt ttttaatact tcctttacta ttccctatat 540

tgcagaatga taatttgaca tgcaagttcc tatgatgtgg aggattttta atcttttaa 599

<210> SEQ ID NO 100
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 100

tgattgcagt ataaggggggg ggagtatgaa ataaataaga attattagaa aaaagggact 60

cttgataagg ggaacaggag tgattattaa gagttctagg acttgcagtc atcataaaaa 120

tcctgtgcga atccctgcac tgagaagtga tgctttgtgt agtaataatc ataacaccac 180

ctgttttccc tctcctagga ctacagagac atcattgaca ctccaatgga ttttgctacc 240

gttagagaaa ctttagaggc tgggaattat gagtcaccaa tggagttatg taaagatgty 300

agacttattt tcagtaattc caaagcatat acaccaagca aaagatcaag ggtatataat 360

tacattattt tcttttatga ctagattaag ttagaggagt gtgttaaatg actaaatgtt 420

gctttactta aaatttaggt caaagttaac tttctgttac attcttaatg ttgtcctact 480

-continued

ggaaaaagaa attatacctt tctactcagc tccttgtatg aaataacatt gatgttatct 540

ttgatgtctg ggaatggtta cttttcttga agtagtgcgg ttgatgcaaa ttgtcctgg 599

<210> SEQ ID NO 101
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 101

ggaagttttc ctttgttccc ggttttctta ggggttttat aatgaattaa tgtctcactt 60

cttcagattc tgcatttgtc tatttgccat ctattcacag gccaatgatg atctggtacc 120

tgggggggcct tacagacctg ggaaaagatt gccccttcct gggcagtctt agtgaggggt 180

tccactgaga acatgtcttt catatacata ccaatgaatc ccaagtataa agccacaatc 240

agctcctttt ctcactctca cacactaagc cagtatttcc ctgttttaaa tcatctcagr 300

gctgggacca gacaactaga tacctgtgcc ccagggccca ctggaattat tcaaactagc 360

caataataag ctgttaactg tgacctgcct tgcatttcct gcagaaaccc caataaagga 420

tttctaagct tttccctggt tttggtctct cctacccaac caaaacctag cacttccccc 480

gtggccctgt gtggcatgtg gtaagccccg acttttctgg gactcttttt tactttttt 540

tttttgttgt taatgagata gggtctcact ctattgccag gctagagttc agtggtatc 599

<210> SEQ ID NO 102
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 102

aaatcattag ttcattcagt taaggattaa catttttcc ataatggatt tctacacaag 60

ggtggtgcaa atttggattc taagtccatg tatagtgtaa gtttaggaaa atttctcctc 120

tctgacacta gaaccactgg gggaaacatt ctttgttgtg aaaggaatta ttcaattctt 180

cttttcattc agggtacagt tcttcaatat ttctggttta gggttgggtt tcagctccaa 240

attccttttt caccactgcc caaggactca attatctctg tatagtgtta atacttgtgm 300

ctctagaata aaaacattgt cttatttcta tctcttcttt tctgtgcaaa gcccagaata 360

caaacgctta aaacaatgaa taaactgcaa cttatttttc aaaagaatac atagctgagc 420

ttgcaagaac caaagcgaaa tccataagtt gtgaaaacac agagagaaat gaaagccaga 480

acattatagc atcagctcag tcccaggttt tttgaaaggt gaggttctaa ttagctcaat 540

ttatcacgcc gctggaatta aagatttctc ttccacattt aacattctat gtttctggc 599

<210> SEQ ID NO 103
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 103

ataaggctat tcctataaag tgttggcatt ttataaaata cttcagattt gaatattcct 60

caatctccgt gtccatccag ctcttcttac tcatgttaat ttctctctag actctttgca 120

gctgattctt tattgagaga gtgggttgct acaaaccacc acataatcta gttacttcag 180

aagcccagaa tttagataat caagttttgt ggtcactgtt ttcttttaac aaggcagagc 240

aattaatata ccctctcctc tccccttaag aagatcctct tttgtgtgtg tatattaagy 300

tgggggagac cagtacaagc tacccatata attataactc agctttcaat cctcctcctc 360

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caattcatat catgtcagcc tgaatatgtc aagtgtttta aattgggttg tggaggaccc 420

agttttttca gagatgcctc tggcacttct aggaggccct tattctaaaa ttcagctaac 480

ataacctaat ttataactgt tttaaatagt taagtcctgt gttaagacca cattcaaaaa 540

gagattccac ttaaaatgtc tgaaaccact gacttaggat attgtgaaaa aaaattttt 599

<210> SEQ ID NO 104
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 104

tcttactcat gttaatttct ctctagactc tttgcagctg attctttatt gagagagtgg 60

gttgctacaa accaccacat aatctagtta cttcagaagc ccagaattta gataatcaag 120

ttttgtggtc actgttttct tttaacaagg cagagcaatt aatataccct ctcctctccc 180

cttaagaaga tcctcttttg tgtgtgtata ttaagttggg ggagaccagt acaagctacc 240

catataatta taactcagct ttcaatcctc ctcctccaat tcatatcatg tcagcctgar 300

tatgtcaagt gttttaaatt gggttgtgga ggacccagtt ttttcagaga tgcctctggc 360

acttctagga ggcccttatt ctaaaattca gctaacataa cctaatttat aactgtttta 420

aatagttaag tcctgtgtta agaccacatt caaaaagaga ttccacttaa aatgtctgaa 480

accactgact taggatattg tgaaaaaaaa tttttgttgg agaataacag tatttttcca 540

ttactttgtg ttctgccagt tttttctata ctcgcgtgtt gctttactta cctagtgtc 599

<210> SEQ ID NO 105
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 105

tttttggctt atgcaattgt gcatgtgtgt tgtatttttt acaaacaaac aaaaatgggc 60

aatgaagtgg aaagaaaata taatctccag gctttggtcc caacgtcctt ttctcagtgc 120

aaggaagatg tcatactcac tgcctaaggc taattattaa atcctgaatg tgtcaggcca 180

tatgcataat gacagttata ttatcattat taattacaac tatatcttca ttgagctctt 240

atatgtgtca ggctctacaa taagcacttt acacacatga tgctatttaa tcttcaaagy 300

agccctataa ggaaggtatt agctttgacg gtttctaagg ccgagtacta aaaagttggg 360

gtgtgaggct ttatggaact tgccaagatc acataaaaaa tgacaagtca ggatatgaac 420

tgatgtccgt ctcactcaaa agcatgacct cttaactatt atgttacact ttaaacactc 480

tgctaaagtt acaaaagtgt ctctgcctcc caaatgcaca ctttcttggg tgaatagtaa 540

ttaataaaac aatttcatgt tttgctgtaa taaattaatt tcaatcaatt ccaagtagg 599

<210> SEQ ID NO 106
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 106

agcctaacac acacttacca ttattaggta taagctccat atcccaagga ctcatctttt 60

ctgtatctcc attgtcccag cttaaagaaa gaaaaatcat tatattaaaa aatctaaatt 120

attgtatcac aattttaata aaatcaatta tcaaaataat tgcttctgtg tttaaaagaa 180

gtctctttat ctcttaatag atggaaaaaa aaattcaaag caagcctagg tgaactaaaa 240

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tacaacaaat atttccttac caaacattgt agcattgaaa cagactatca gggtactcar 300

gttgaagagg ttcctggctt tcgattgttc caaaccacca ggcatcatct atgacagacc 360

tgaagcggtc acctggccaa gaacaaaaac taactcatca ttctgaaatg catggctgct 420

gtcactgctt tttcctaacg ttaaccttta agtacctaaa ctgcctgtat gatttcagaa 480

gacaaaaagt gaaccacaaa ctccaaaaat aagtaagtac aatcagcaat accaagagaa 540

aaaaggaatt tagtaagcat acttgaagtg tgacttaaca gttttcaatt ctatttttt 599

<210> SEQ ID NO 107
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 107

gaagcggtca cctggccaag aacaaaaact aactcatcat tctgaaatgc atggctgctg 60

tcactgcttt ttcctaacgt taacctttaa gtacctaaac tgcctgtatg atttcagaag 120

acaaaaagtg aaccacaaac tccaaaaata agtaagtaca atcagcaata ccaagagaaa 180

aaaggaattt agtaagcata cttgaagtgt gacttaacag ttttcaattc tatttttat 240

atttcattaa ggtatacaga aattcacttg ttttaggcat ttttaccaat ctagcatttr 300

aaattcatca ttaacactat acccaaactt ttcactgaaa taaaattata attgcggcaa 360

gttccactca acaattactt agtcttttaa tttcttactt tctgtaagca agtttcccca 420

accaacaatc aatcaagact ccacgctaaa aacaacaaac aacataaaat ccaacctgtc 480

ttccttcatc tcaatcaccc ttaatactca ctcactctcc ctttcctgta aaaggaaaca 540

aaaaagaaac aaaaataaaa caactattct ttttaaaaca gaggacactc cttgtgtct 599

<210> SEQ ID NO 108
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 108

cagatgtacc aaaggctgat agccaaaacc aagaaaaatg ttttcatcta ttttacctac 60

tacttcttga cttacagatt tcttcactca tcaatttttg acagtaagta tcagagttga 120

ttcttgaaga catgggtttt aactgaccag gtctacttat acacagattt ttccaataaa 180

cagatttggc cctctgtatt ggcagattct gcatcagcaa ccaaatgcag attgaaaata 240

cagtattagt gggatgtgaa atccatgaat atggaagggc caacttttca catcgggggr 300

ttccgtagga tcaattctgg aacctatgta tgcaaagatt ttggtatcca tggaggtcct 360

ggaagtaatt ccctgtggat actaagggac aactataact tcaatacaac tgtgcataaa 420

aagtatgtgt attatattta atccatattc aatttttaat catgactgtg taaatactgc 480

ttgctcctaa gcaaaacagc atataattcc ttccttatat aattttgttt tccctaaaat 540

taataattgc ttcatttttt taatgcttgg ttttcagtga atttacaatt aaatcttcc 599

<210> SEQ ID NO 109
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 109

tttaatccta gttatagtaa gttacaacta aataaggtat tctcatagga gttgagtagt 60

gcaacatgta gaaagctaat tatttccata agctggacat tacacttcta cacagcatga 120

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gaaactatgc ctctgagaaa gttccttaac tttgctggtc acccacaagt ggccacaatg 180

gtcttgatgt tgttacctta gactcaggaa aaaaatgaac tttctaagaa catttgaaac 240

ctaatatttt tacaagtaaa aaaagttatg caattgatta aagtcttttg tgaatcacay 300

gtaaaacatt aaaaatgatt gtacactaag actgctacat tttacttgtt tttttaaaaa 360

caaggtagtg taattatcag tataaaataa tacttgttta ctaaaagaag caatgccata 420

acatgatatc agagaacact acttgcaata ggtaatacta ctacttccca actgtagtag 480

ttgtcatttt cctctttttc ctattagcca cagccacact gagtgtttct cagtcaaaca 540

tatcaagagc attaccctgg agagttaggg taaaggtctt tggaatttac tgtacgtga 599

<210> SEQ ID NO 110
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 110

ttaaagaata gaccctaggg agaaacaagg agaaacagga agacacatga gatgctacca 60

cagtaatata aatgagagtt cagggtgatt cacaccaatg tgatggcagt ggagtggtga 120

aaaacagtaa agtgctgaat atacttataa tccattagat aattaattcc ctgatggact 180

ggatgtggaa tatgagagaa aaagaggaat caaagatatc tccagggttt ctggtataaa 240

caactaagag agtcgtcata ttactgagat aaagagggct ggggtacagc gggtttgagr 300

aaaaagcttg gtaaataagt tttgtaggtg ttggatgtga ggagtaaaat gatatccaaa 360

cagtaatttg atatatacac agttatcaaa taaagtagcc attatgttat gcactgagta 420

tatcacagag atcccacaac ccaggaactt ccactgtgct ttattcagag cagctgctat 480

cagttttgta tactgaggag ctaaaagttt gtttgaaaaa ggtttccttt gactaataaa 540

aaggaaaaga aagacagaaa agtttgaaaa tcataattct agcctcaata tggactatt 599

<210> SEQ ID NO 111
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 111

cagcgggttt gaggaaaaag cttggtaaat aagttttgta ggtgttggat gtgaggagta 60

aaatgatatc caaacagtaa tttgatatat acacagttat caaataaagt agccattatg 120

ttatgcactg agtatatcac agagatccca caacccagga acttccactg tgctttattc 180

agagcagctg ctatcagttt tgtatactga ggagctaaaa gtttgtttga aaaaggtttc 240

ctttgactaa taaaaaggaa aagaaagaca gaaaagtttg aaaatcataa ttctagccty 300

aatatggact attaattgct aggcaaggat ttctccccat aaggaattta tctatgttca 360

atggggaagc taacaacttt tacatcaaga caggtaagtt gtatattaaa taagaataat 420

catatgtatg actgaaagac tttgggcatc accaaaaatc attatgagga catatcttat 480

tccccaataa ttcctgagga acttagaatg tttggttgag gaagatttct gtcacttatt 540

aattataacc attaaggggt taagaatgca ttgagtattc tttaacattt ctagctcca 599

<210> SEQ ID NO 112
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 112

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agatagttaa ctcaggaggc ttgcattgct ttcttaactt catacttttc aaaaccagta 60

atgaaactgg tttgcaattc aacattataa cggtattcag aagaaacaat actaagatga 120

taaagttaaa agcatcattt tgcagatcta gttgcaatca ccaaaaaatt attttctata 180

gagaacatat atcagaaaat ctacatttca tacaacttca aaaactctct gaagaacttt 240

gaacttacag agactttgaa acgtgttgct ggttaaaaaa aaaaacacct ttctaaagay 300

tttatataac atttggaaaa ataaaaagca ttcatttacc tagaactgcc atcactgtgc 360

catgctctct cttcttcttc ggatgttcca ccactgacag caactacttc gccttcctaa 420

gatatgttga atacatgtct tattgcataa ttttataaaa taacatttta tgattacaga 480

aaatatcagt gatatcttat aatatcagtc atattgggat atttaaaatt tgatttaaat 540

tagttgcaaa gggtgttgtg gctcacgcct gtaatcccaa cactttgaga ggtcaaggt 599

<210> SEQ ID NO 113
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 113

ctcaggaagt acgtatctct ctcaattagg ccatgaccaa ttgaaatcta ctgggtgcaa 60

cagtttttcc agagtaggat gacagaaaag ccaataagtc aaaactatta gggacaatct 120

acctctctta atgaagaaaa tgagaaatat tatctatagc agcattagct gacttgatta 180

tctagaataa tgaatagatg caagacacca caaaaacaca tagaaaaaca taacaaaatg 240

ctatttttag actgtacaaa gatggcacac aagattatga agagctaaag aaagttctts 300

atgaggcttc agtgtaattt attagaattt catgagtatg taagaattgg cactttggga 360

aagggtatgc tacaaagcag aaatggaatt aaaaatttta aatagtaaac aatagataat 420

ccagagataa ccaagattta ctatgttaat ttttatcatt aacctgttta taataccatg 480

ttaaattaca aaatggagcc ttaaaatggt cactatactt aagaagcaaa tattaaacat 540

caaaataatt aatatgtacc tttgagacag tgggtatttt attctctttt ggaacagtt 599

<210> SEQ ID NO 114
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 114

ctctcctcag gcctcactat tccctgagac agaacaatat taaagttagg ccaattaaaa 60

accctaactg atccagtgaa aacatctctc actttaaatc aaaggtagca acgattaaac 120

tctgtgataa aggcatgtca aaatctgaga caggctgaaa gctatgcctc ttgtgcccaa 180

caaccacgtt ttcaatgaaa aggaaaagct cttgaaggaa gttaaatatg ctactccagt 240

gaacacagga atgatatgaa agtgaagcag gcttgttgcc gatacagaaa tagtttttgy 300

ggtctggata gaagattaaa ccagctacaa cattccctta agccaaagcc taatccagag 360

caaggctcta actctattct cttctatgaa ggttggaaga ggggaaaaag ctgcagaaga 420

aaagttggaa gctagcagag gttggttcat gaggcctaag aactacctgt gtaacataaa 480

agtgtagggt gaagcagcaa gtgctgatga agtagctgca gcaatttatc cagaataact 540

agctaagatc actgaagaca gtagctacat taaacaacag actttcaatg tagtaacag 599

<210> SEQ ID NO 115
<211> LENGTH: 599
<212> TYPE: DNA

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 115

gaagaatgca gtgatatttc actgtggttt caacttgtat ttccctagtg gttaatgaca 60

ttgattatct tttcatgtgc ttatttgtca tctatagatc ctctttggta aatgtctgtt 120

catgtctttt gcccattctc cggttggatt ctgttgttta ctattgagtt atgagaatta 180

tttctatgtt acttagcccc ctgttgggta tgtcattgga ttccatttta attaatggat 240

gaggctgacc catttcagag agccttttta aaaggaaact ttagactacc cactggagas 300

attcttagga agattcccat aggatgagta caaagtttta gagacaaagc tccaggaagc 360

ccaaagaaag aatatctgtt aaagttatgg ccacagtctt gcttgaccat aggccaatga 420

atagttaagc ccaatgataa aggaataaaa ggatgaagaa tatttgaaga gaaataaatc 480

ttcctcactc ctcaggttcc cttccatgtg caggagcctc aacctacaac tagcaacctt 540

atctcctgac tcattcctct ccagaggagg agtaaattag tcaactgata tgctctgga 599

<210> SEQ ID NO 116
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 116

cgtactgaga cacattaatc tcacaaactc cagataagtc cactggactg cactactcta 60

ggagtagcag caggaatgat tcctctaatg cttcttctca ccctccattc taagtggacg 120

tgtctaattc caagaggagc cccttctatc cagtatgtcc atctttattg caacttcatg 180

ctaaatcctt taagaaaaat aagatgcacg tttgaggttg atttttctg tgctccttac 240

agaatctaat ttcattattt aaaagtcact caacacaaaa gctacttaga agcttttgty 300

gattgaagtc tagaacttaa aatattttca taaatatttt tctagtctaa aaatatagta 360

gaagtattca taatgacaaa actggtttaa ccttctttac agaacctttc cttattttta 420

cttaatacac tagtgctgca tttcttgtca aaagagggaa agcagtttgt agactttgac 480

tccattttaa ctctcattta attcttcaac actccattat acttcactaa aacagctctc 540

aacactttcc atgtcaatcc tcttataaac ctttaaaagt tggtaacttt ttaaaacat 599

<210> SEQ ID NO 117
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 117

agaagccaag agagagaaca aaaaagcaac tactttataa atctactcta ataaatgttt 60

ccagaagtat aattacaagt ctaagattac aatttgaagt agagtggaga cttgaaagta 120

gtccaattta gcaatttcaa aggaaatctg ataaatgttc ctaagcatgg tatccttcat 180

gtgttgttta aacaaacatt ttttcttttt gggggtgagg gttgcggggc aagtaggact 240

gatcaaccct tgaccctatt atttatcaat gttgccacat ttacagttag tagatctctr 300

aaataatctt ggggacagtt gaagcttata aagctctaaa agagcaaaga aaaaatagca 360

atcatattta agatgcctgt gtgtcctata taacacattt cattgtgaat atggcaagac 420

agtattaatt ttcttggtat aaggcatctg tttaactcca aagtgacttt tatatggaga 480

aaatgaaagt atatttcaat catatcagaa aaaagaaaag gatattattt ggattaacca 540

tttgtttact aaaggaggca ttaaaagaat ctgctttact catgaaccag ttagaaaag 599

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<210> SEQ ID NO 118
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 118

tccacatagg tagttcaacg caataaacat tattacaaat gaactgaata aagaagtcag 60

ttctccctta tgtctttcat atttccacta ataaaaccat tgttctcaag gtcacccggg 120

cttaacactc tataaaccca tttattaaat ctttcctccc tgtcatccta tagcccaaat 180

cctaatatag tcacaaaaca ccaagtcatt tatgtatttt tttctttaca aatttcctac 240

caactacccc tataatattt catgactaat taaagtagtt gtcctcacac ttattcaatk 300

tcatacctga aattgtacta ctggcaacca aactattttt ctcttagctt ctcgaccatc 360

ctataaaata atttactaaa gcccccacaa ggttcatagg tatttatgcc tatgagatca 420

tttgaagtca ctgacagttc atctcaattt gtttttcgtc attatttcca aaatctactg 480

caatcaagct tcctaaatat ctaaatttct atgaacatgt cttgacactt agctttttat 540

aatgttcctc ttgtttataa aattcattct ctttcttact gactcgattc ctatttatc 599

<210> SEQ ID NO 119
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 119

tagttaaact cgtagttaaa acttagctgt ccggtgctaa tttaatgggg aataaaagac 60

cataaaacaa tttatattta ggaacattta aggttataat taacttctaa acctggcgac 120

ctctttcaca gaaggccctc agcttcagtc ctgagagttg cacacatttt caagctattt 180

ctgggaatta tttatctgcc ttttagcatt taatgggagt atagagcctt tagagtttag 240

aacaactctc atcaaaacaa agctattctg atgtttacct cctgccaatg ccaaacaaaw 300

gtgggcttac taagttatac ccaactatta tagtttggaa tattcttaat atacactact 360

tgcttcagta aaatatccaa atatatacta catttcctct gaatactcaa gttatgtaag 420

gactgttcag ttgattcgta aagaaataaa agtactgaag gcctagaatg tagtttgttt 480

gtttttaaag aataaagttg tctcataata ttttctacaa aattctcttt ggtttcttct 540

cctgttcact taaaaaagaa aaacaacaac aacaaaaaga accacaaagg ctttcccaa 599

<210> SEQ ID NO 120
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 120

attttagtaa ctgaaaaact tattgattag ctacagagag ccaaatagct ataattatag 60

ccaaaactca acattcatga tagcaagcag tgagaacgca ggccctccct cgaattgttt 120

ctctttattt tcttaatagc aatgctggat gctttatctt ccatttgccc ataaataaaa 180

caagcaatga aaagaacaaa agagtgaaga gcaaaaagaa ttagggcaat tagataactc 240

ataaaagaca gacaggaaaa aaaatcaagt taaagagtaa gatgtcaaaa gatccactcr 300

gatttattac cattatgaaa acatttcttc atagacatat cactaactga gtattgttaa 360

aagttagcta tgcagtaaca ttgacaaaag ctcaaaaagc caaccatgac aagatttgag 420

tacaaccaga gtcatgggtt tatgctccaa gtgcccgcat aatagctgtg tgaactcagt 480

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aaattggggc aaagcacttt atctctgtaa tgtacagttt ctccattcct aagaccaaga 540

ataataaaat ctatcttgat catcttacaa ggttttcatg agacccaaag gaggtaaaa 599

<210> SEQ ID NO 121
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 121

aggtatctct aatatacaga aagtagacat ttaaaaaata tgactacaca aactgcagta 60

gttgaggaga ccttaatact tcatacagta aatagaaaca ctgctcggta agttgtatgt 120

gatatattaa aacattgtaa ttcaaatact tggccaatta tgttaacatc taagaaacaa 180

aatgtgaaga gaagagtata aactcaaata tttaatatac taccaattga ttaaaagcaa 240

gaaatgcttg attctttggc cttaatttta aaatcagtgt acttgagtaa aattctattr 300

tgctagaaga ctattaaaca agtacaataa tacgagtatt tatttataat ttcttcacat 360

ggttttccaa gtatttttc ttctctatat tgtatcttca tacttgtgaa tttccaaagt 420

ttcactgcta aaactgataa aactgtatca gttatcacaa tgtacaggca ctgtaatatg 480

cacaattaat tttcttttaa attcagcatg tcaataaaag tgtggaataa atcattcttt 540

attgatggga atttaaagtc aaaataatga accaattttt aaatggattt cctttgtga 599

<210> SEQ ID NO 122
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 122

aacatctaga agttagaaaa tgaacatgtt tggatattag tatggcaaag acagactcac 60

ttcattagtt tgctatccct tatctcaggt aatactccta tccacaatta taaaatgagc 120

ggaaaaagta aaactgaaaa taaaggtagg aggaacaggt attagacact atttggatct 180

actcatgttt catttaattt tcttatcaat ttactacaaa taaccagatt ttttttataa 240

cttgtttaaa aataccctaa catccattca aaatgctgct gcataaacac aaatctgaak 300

tggaatctta gcactgctat acaatcactt tttaaagtgc aaataagaac aatatgtagc 360

gaattaactg ataaagatgt acaaatatga atcaaattta ttttacttaa ctatagaata 420

ccttcaaaat ccatgaaaac ataaaccaga tttaaaatac cattcttaca atgaaacaac 480

tatttaaaca ttcattcttt aacagggtcg attttgaaac tatttattct ctcctactag 540

aacattatag tcttcttaaa gaaaaacagt catgtgatta tataaactaa actcttgca 599

<210> SEQ ID NO 123
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 123

caggagaatg gtgtgaaccc gggaggcaga gcttgcagtg agctgagatc gcgacactgc 60

aatccagcct gggcgacaca gtgagactcc gtctcaaaaa taaataaata aataaataaa 120

taaaagatat ggtatagaaa gcatcaaagg gcagagaagt gctctagtcc tggccttgcc 180

aatttttaaa catagtttta actatgggaa agtcatttaa ccatttcagt gcccttaatc 240

caaagataat actatccagc caacttgttt tgataaaccg aagtattaat atgggcgacy 300

gcacaaatgc aaaatgttat tatggggagg gaggggaata catctatcta ccttgatgca 360

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gtttagtgaa acttcaatga ttctgtctcc ctacattttc ctagatctaa aataaaatct 420

aaagtttata gattcagtag catcaataat taaaattatt ctaaagaaca gcattagaaa 480

ttcttaagat taagttctga gcatcaaaag cagctattaa aactatgcag cacatagaaa 540

ggagtggtaa taaaacaggt aaatgctgaa ggaaagagct aggattagga taaagagaa 599

<210> SEQ ID NO 124
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 124

tgtgacctcc acctcccagg ttcaagtggt tctcatgcct cagcctcctg agtagctggg 60

attacagatg tgcaccacta cacccagtta atttctgtat ctttactaga gatggggttt 120

cgccctggtg accaggctgg tctcgaactc ctggcctcaa gtaatccacc caccttggcc 180

tcccaacgtg ctgggattac aggctataaa tgtgttttaa ataaatgagg aagaatgaat 240

taaaaatcga taaatatgat tattttaaaa aagaccaaaa tgtctaacat aatttgaacr 300

gatacactct cttttccata agcctacctc tagttccacg aatgttacta agatcaataa 360

gccaaagagt aagatattat agtcttttga ccaaagaaaa ataaaatgtt aaaaccaagt 420

tatggatatt aaaaataatg ttacgtaaat ggtgaaaagg ggcaatgaca taagatatac 480

ctcttctaag gtgtatgaaa gaaaaggaag tagggagaga tcatgtaacc tcagcaaaaa 540

caaaacaaaa caaaatctga ggattaaaag tgagagggag agaacaacaa gcgaatgaa 599

<210> SEQ ID NO 125
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 125

catttgtgtg ctcactggag tagcacgttt aatttccttc aagaactttt gctttacatt 60

cacaacttgg ctaactcttt taacatgcat tcctcactcg ccttaatctt ttctaacttt 120

tgaattaaag tgagagacct gagactcttc ctctcacttg aacactaaga ggccattgta 180

gggttattaa ttggattaat ttcaataggc aggcccaagg agagaaaaat ggggaagggc 240

cagttggtgg agcaatcaga acacatgcaa cattcattaa gttcgccata agggtgcagk 300

tcatggcacc ctaaaaagac ttacaatagg aacatcagag attatagatc accataacag 360

ttataataat aatgaaaaag cttgaaatat tgtgagaagt atcgaaatgt gaaagagaca 420

agacttgagc atatgttgtt agaaaaatga tgctgacaga cttgctttac tcagggtttt 480

cacaaatata caatttgtaa aaaatacagt atttgcaaaa tgcaataaag gcacaatgaa 540

acagggtacg tctgtattag cattttttcat aaagcctagg cagtgtctag taacacatt 599

<210> SEQ ID NO 126
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 126

ttaaagaaat caacgactaa cattgattaa cactgaatga ctaatattct ttgagtgtgc 60

gggatggcaa ctaagaaaca acttgtccaa acactgaaac tccctctact tatgagatag 120

aactggctga aatcagttgg aaccaagatg gccaactgga gtctgcacag aacaagcttg 180

ctgacatcat agcctgacta tctaccacat ttcatactaa ctaccctaga atttgcacat 240

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gtgacccatg aggtatcata atgagttaac tgtgcatgcc cagggacatt ccagacctcm 300

cctttccttc caccaaacac ctactaatct cagaattcac ccctactgaa cctgtaataa 360

aaatactgcc ttgaaaccag catgaggaga cagatttgag cttgacccct gagtcttctt 420

gggagttgac tttcaatata aagcttttct tttctcaaaa acccagtgtc atagtattgg 480

cttctagtac actgggcagc aagccccctc tgctcaataa cacaagcaga aaactgtaca 540

cattgggaaa cagtttactt ctgttcagat aacttgagaa accttaaaat taaaatatt 599

<210> SEQ ID NO 127
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 127

tgtgacccat gaggtatcat aatgagttaa ctgtgcatgc ccagggacat tccagacctc 60

ccctttcctt ccaccaaaca cctactaatc tcagaattca cccctactga acctgtaata 120

aaaatactgc cttgaaacca gcatgaggag acagatttga gcttgacccc tgagtcttct 180

tgggagttga ctttcaatat aaagcttttc ttttctcaaa aacccagtgt catagtattg 240

gcttctagta cactgggcag caagcccccc ctgctcaata acacaagcag aaaactgtay 300

acattgggaa acagtttact tctgttcaga taacttgaga aaccttaaaa ttaaaatatt 360

gacctatgta cctaaaagag aggcataaat tatacaaaga ttactacttt gacatgaaaa 420

taaaagaaat tatgtgattt tttaactaaa aatatcttag agaatttggc attccttgaa 480

aacctactgt tatctggcag agtcaacaag gagaatttta atttctcttg aggctacttt 540

acagcttttg agtcagagat ctcatctctt attgccatta gaataagcag tagaaatga 599

<210> SEQ ID NO 128
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 128

actgcttaaa acagtggctg gttcataaaa ctctgaagtt cattaaagga atgcataaac 60

tcattttctt tattatacca tattaattag aatcagagag acaatttatg tttctgaaaa 120

ggggggaaaa ctctgctttt tatatggcgt tccatgtact tttgagtgcc ttagttgtga 180

aaattcatta actctgcttt tctccgttaa atgtcactta aggaaatgat tttaaaacca 240

agtaaaaaac attaaaaggc taaaagagaa ttagtgaaca aaatctgact tggcaattay 300

gctatttccc tccttgggtt tttctcatta aaataattgg gaaagcaccc attcttaaaa 360

tactgtcata caaaataatg atacattttc ctaatacaga atttcattat caattacaat 420

gatttccttt ttaattcttg tataccattt ataaataaga ttttatttgg ataaaaaata 480

aaagataaaa tttacttaaa tctataagta gcagtaggaa aaacctaatg actgctttct 540

attttgttca gtactaatta tatgcattat ttcatgtaat cccacaaaaa tcctatgtg 599

<210> SEQ ID NO 129
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 129

caagagaatc ccttggaaaa agctttcaaa tatatataca caaatatctt agaaataaat 60

ctgcaaggtc ttaaaatacc aattatataa aaaggaaata ctggttgatc cattaccaaa 120

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ttgttacctc caaaaataat aacagtatgt tctctcacag gagtgtttca ctggtcaatc 180

atgatctact atcttaaagg ctgattctat ctattttcaa gactgatttc cataggacta 240

gttagcgtct agtctgtgcc tagtgaaatg caaaaaacac tcagcaccca ctttattaay 300

gagcaatatg aatagtgaac atatgtgtac cctaccacca cttgaagtga aaataataaa 360

aatacaagaa tttttcaaaa aaatagtgcc ctcatatctt cgttatttct tattgtaagg 420

taacattctg aaatctgtaa ctccaaacca ccagtaaaaa attacaaatg agactgaatt 480

tagcaaaaca aattctatca cattcttaaa aaataaacat ctttagactt tggtaagacc 540

atataaaata gtacagtgct acttttcttc tcttaattga tgtgctttca actaaagaa 599

<210> SEQ ID NO 130
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 130

ttcacctata agcaatattt cctcaattac atatatgaat ataaataata ctttagcaat 60

tacttacagt aaatatccgt ctgccagttc gatcaaaagt tacacagtac acagatgaca 120

agtgtccaag aattcgttta tgcattttca tgtgctgata cactgcagtt ggaacaagtc 180

gctcaagtct gtatttccca ttcagcttcc ttgaaaacag agtatccgct accaagaaaa 240

agaaggaaaa taaatgtaat ctggaaatta attttcttac atgatcacct tttaagaaty 300

cacatactcc aatttgtcat gtgcaggtaa aaataaagaa gctttctgat atatatggct 360

tctagttaaa agtctttaaa gtaatgaata aaaacattgt ttcacctgaa ataagtcagg 420

cactatcatt ctcactttat aacttaattt gtaagttaaa tgacctgtcc aaaaatcaca 480

aagtaaggca tgaagctagg attaaagctc agatttattt actctctggc tagtgctctt 540

taaaaaccta aagcatttat atgttatttc cttaaaagct gtctatgaaa tagtttttc 599

<210> SEQ ID NO 131
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 131

caaaggcact taaaactgga acccagtgta cttttcataa atcagtaaca cttgaacact 60

cgaaatctga catgcagaat gatatttaaa aacatcttta taacaagtga agataaagga 120

atacgtcatt tgcattatta aaaaataata attaaactgg gaatcttgcc aaacacctgt 180

ataatgattc cttctctgga atctattagc tctcccttag ttctcccttt caactcattc 240

attctaatca ttattcaaga tctgactgaa gtttatcttc tgtcccaaag cttgatacay 300

tgactccagc tgaaaatgtc ctcttccatc taaattacta ctgtacttat tttctatact 360

ggtaacttat ggacaaagaa ggtgctcaat aaatatatgt tgactgatct gcaggcacat 420

tattaaccta cagatgatct tctaatacag gctttttttt ttttttctaa cagtgactgc 480

catctacatt gggtaattag cactagggtt tctcggtcga atttagccct aaagaaaact 540

aaatatatat acaaaatact acttagccaa ggtacagagc ccagtaatta tgccctaaa 599

<210> SEQ ID NO 132
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 132

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aaaggaagat ttatctcaca gattaaaata ttcaaaatat ctctaaatag tgcttcattt 60

taactgccct gctaaatgaa tttaattggg aaataagggg agaacgtatt cacttaattt 120

tctgaatata gaggataaat gaaataaaaa ttccagaaat cactgttatc catttgaata 180

aagtctgaag taaaaaagga gcaaaatact gaagcatgtc atttgcagca aatcattcag 240

aacagccttt gaaataaagt atatgtgctc aagtctacaa agccaattag tagagatcar 300

caaaaggccc acaacttctt aaacattaga tgtgactatg cgcatattca gcccttgggt 360

tctcatccat tacttcttta ggtgctagga taataagtca aattccccca taagtcactt 420

cttacttcac acctagttat ttttcgagaa ctgatttact tatccaatca taatactaat 480

gcatattcaa tttagaaaag aacataaatg aaagaaaaac ccataattct attgtctata 540

gcaatcactt ttaaaatttc gcaaaggttt acctcaaaaa cagcatttta acagctatg 599

<210> SEQ ID NO 133
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 133

tttaacttta ctaccaaact gacatctttc tatctagaac atggtgcttt cttcctgttg 60

ttgggcccaa attttcaatg cagatgattt tttaaaaaga taaacataat aaagttacct 120

cattttctct cactacatca tttgaaccaa gttcacaaag aaagaaaaag gtagctgcca 180

taaaagagta tctgtaataa ccttagtaaa tacatttttg aaggcactag aaaaatacat 240

gataaaaaaa accctgcaaa taagtactat agcagaaata ccattacctc cctacaaaak 300

gtttagactt ttttctcctt ttgcaaagat ctttgtaaaa tgaacaagca cacatgataa 360

agctgcaata aattacccaa gatcaaaatt aaccatggtt aaaaaagatg acttggaaaa 420

aaatgaaaat gactatgaat taacaaaata caaaggttag tgtttttgt tattattgtt 480

ttctaactgt taataacaat ataatatgct atataatacc tactccagtg taggaaagct 540

gttccctctt aatcagaaat ggaggaccac aaaaacagtg cttacaactt ctgccaact 599

<210> SEQ ID NO 134
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 134

ggttctaaac acgttggggc tgaggggtgg atatctggga gtctgggaaa acttctctga 60

aaaactgaca tttaaactaa gacctgaaaa atgaacagcc acagaatgct gatgtgagcg 120

cagcatattc caggttgagg aaacagcatg tgcaatagcc tgaggctgga aagagcatag 180

cattcaagca acatgaagaa gtcaagattg acttgcacac agagtagaga aagggcaagt 240

gtcaagagaa gagactgaga aggtagggga gcggactata tagagtgctt tctaagctar 300

gttaggtatt ttggactaaa ttccagtaat aacgggttga agttttgggg gagaaaagaa 360

tggagtaata tacatagtaa gatttacttt gggataactc attgcagttt tctcttgacc 420

acaatgagaa tgaattggaa aggatataag taaaagcaaa agctaacttt gcaaaaaaat 480

caaagggttc tgaaaacaaa atttcatttt agaaaaaatt taatcagctt gacaccaaaa 540

ttatcaacac tttcccaagg aattaaatac ctgatctcat aagtatctgg cactatata 599

<210> SEQ ID NO 135
<211> LENGTH: 599
<212> TYPE: DNA

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 135

cctagagata aaaagtttac tttgctaaca tgtcaaatgt aagaaaaatg caaacaaagc 60

aatcagcaga aattgcttta atttaatgta ttacaatctt tttcacaaga taaacatgca 120

ttaaaccaac ttccaaattt aatcttaaaa acccctttaa tgtatttagg tctcttcttt 180

cctatctccc cttactcatg cacatttatt actgaagtat aagcaaatat agaataaact 240

atatctgaaa acaggcataa tgtgggtatg gaggtaagag aaaggacaat actaaagatw 300

cgctaatacc tttggaagta aatgctgcta tgccaagtac acactcacat ctctcttcca 360

caataaaaga atcacaagct agtaataaca acagatcagt gggatctttt gtctttgctt 420

ttgaaaacag tattaaagga ggttctagag cactggaagg caggtgaacc actttgggtc 480

tcttgctgag actgagttct agttcaattt tcacaactta catcaaagac caaaaggttc 540

aaagtagttg ggaattctaa gcacataata aaataaaaca ggataagaaa acactgaga 599

<210> SEQ ID NO 136
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 136

gcatttaaaa gaaaacttac caaaatgagt ttttaaaatc gtatactttt ctttaatctt 60

ccccaaaata atttactcaa aaataaaatt tagaagtcta gaatacttgt aaggttgctt 120

ccagttctaa gcttgcaaat gattatttta atgtgactta attgatcaaa attccttta 180

aaaattttac tttaaagaag atggaagttc attacttatt aacttcagat gtgtgatgat 240

cctgttttag tatcctctgg caaaatatat tttcaggtag tgaaactgaa aatccttack 300

gtaatattct atctttcaat aaaatattat gaatccactc tgactcaagc tttctttggt 360

gatttagaat gtttgaattt ttcaaaatca actttcattt taaagttaga agagatactt 420

ccagttctta aattccttgt gctttctctg gcttttgaga ctttatacaa gctgatgcct 480

ctgctggcaa tcttgtctta cctgctcacc tctacacctc attctccttc atgtctcagt 540

ctatgtctca ctcactgcct tccatgacct atttacacca cctgtgcccc tttttggac 599

<210> SEQ ID NO 137
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 137

tttctcagta atctgccata caatattatt tcaggggaaa aataacccct caagatcccc 60

aatttctgat atacgagtta ctttctgtga ccctaagtgc tttcaaattc ttaacattca 120

agacataaaa agtatgacca gattataaag tcagtgtgat aaattatact aatatagcta 180

acacatattg gctgcacact gaatgccagg ccctatggta agtgtggtaa gttttacatg 240

gaactactca taactctgag aggtatatac tatcattatt cccattctat aaaaaaattr 300

tagaatttat ttaaaaagat attgagacct tcccaagttc aaacacagca cataagagag 360

tcaaaccata gcaatctaac tctggaccct acaattcata ctatcacaca aatgacctat 420

tacctcaaat atgtgtatat atcaatgtgc aagatataag caagtcatac aacagacatt 480

ttgaatagtt ttcaacagac attaaactga gccagaaaaa gagaaacatt tcacagttca 540

cttgcactac taaggaaact agcataaaag cataaattcc tataggtaaa agggaacac 599

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<210> SEQ ID NO 138
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 138

caatttctga tatacgagtt actttctgtg accctaagtg ctttcaaatt cttaacattc 60

aagacataaa aagtatgacc agattataaa gtcagtgtga taaattatac taatatagct 120

aacacatatt ggctgcacac tgaatgccag gccctatggt aagtgtggta agttttacat 180

ggaactactc ataactctga gaggtatata ctatcattat tcccattcta taaaaaaatt 240

atagaattta tttaaaaaga tattgagacc ttcccaagtt caaacacagc acataagagr 300

gtcaaaccat agcaatctaa ctctggaccc tacaattcat actatcacac aaatgaccta 360

ttacctcaaa tatgtgtata tatcaatgtg caagatataa gcaagtcata caacagacat 420

tttgaatagt tttcaacaga cattaaactg agccagaaaa agagaaacat ttcacagttc 480

acttgcacta ctaaggaaac tagcataaaa gcataaattc ctataggtaa aagggaacac 540

tttaaaaaat tctaagggta aaagtagaag ataaaactac aatatttata agattatac 599

<210> SEQ ID NO 139
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 139

gcctattatt tctttataat tataataaaa ttaatataga accttattaa gtgtaaaaat 60

cttgatggtc tatttgctca agtaattgtg aataaacaag cttcaaagaa tatgtcatat 120

tcagaattta cttaactgtt aagaattcat ttagataata attcagttta cattatcaat 180

acaaatacca acacaaattt gtcatttaaa gaaaatgcaa tactataaga aaaacaaaca 240

aaaaaagaaa atgcaatact acgcttccaa attttattca tcataaacca attacatctk 300

gctaaaaaaa agagactcta ttcagaattg aggtttccat aaaccaaagt agggatgctc 360

cataaaaaat aatttaaaat acaacaaaat gacaacattt aactgcttaa aataacaaat 420

tttcaagttt tgatgtttaa gtcgtcatat gtgctaattt gtgtaatttt aaaattctct 480

ttaaagcatt attagtaaaa cgttaaactc aaatctagga atctgatgaa aagttactgt 540

gtattaattt aaggacgaaa catcctttaa ctgcttatac taaggccaat gtaaataat 599

<210> SEQ ID NO 140
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 140

ctagattcac tattcaaact aagaaataaa caaatgacaa agctttcctt tcgtccaaaa 60

aaagtttttt attctacagt ttaagaattc tgatacttgg aaaaagtgcc ccttttcttt 120

aaaataaatc tcatatttta aaaaatgtaa aatctaatta aacgtatacc atagtaccaa 180

aaacaacttt tagcttccta tccaattcca tttactttgt taaaaatgtt ttaaatctta 240

aggtagatgg tgataatcag tcatgtttta taccagagac agaaacaacc ataagatacs 300

accatttcct ttctcaatca cacttgaaat gaacgcatca attttaacct gcaaactttt 360

aaaactgctc ttaaaattct actttcctct tgattaaaat tcaaccattg cgattgtaac 420

tagactaact acagatgatc agtgactatt tttaaattca catctacaaa tattacaccc 480

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cattttaagc agcaataatt tgaggtttcc tagaaatttc aatgcgatgt gatatatgag 540

ttctcccatt taaaatattg ctcagtttat tagttaatac aacaaatcat ttccaggta 599

<210> SEQ ID NO 141
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 141

aattaaatta actcaaaatc aaaattgata gctcattttt actgaaaaaa aaaacaaaaa 60

aacaaaatga tattcctacg aggattagcc attaccataa tttagccaga taacattaag 120

ctgcttcatt taaaaaatgt aacattacca aaagattaag aaaatgcagc attcctcagt 180

gacttaaggt ttgtgggttt ttaagagatg cacagatgta aaagcagatg caaagacgag 240

ttttgtaaaa cctgccccat cttaaaaatg gagtattata atctttgcga taatttttty 300

aaatatcaag gaagacatgt aaattcactg aagacttcta tcaagtattt gtaaacctaa 360

aaattaattt caaattagta aatcttggag tttacttcca gctccattca ctttggccaa 420

gaattgaatg aaagtaaccc aaatcactcc ttgaaaatta acacacgttc agtgtgaaaa 480

tgaatacact aatacactgt taaatctcca ttagatgtat taaacctcag tacccttgct 540

tatttcaaca gccttgagcg gttatcaaca tcttatatta aaccacaaga gatttatac 599

<210> SEQ ID NO 142
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 142

gccctatact aaaacatcca gaaatcatca tacatatgag gaagaagaaa taaagcctca 60

aacccttttgg aataatagga tataaaattg ccttttgtaa ctgaatctta aaaatggaag 120

gttaccatga cttgtcctat tgcaacctgg ttatcagaat aacttatttt ttttaagata 180

gctattctca aatactgaac atatttgcat ctttaaagac actttattct attcaattat 240

aggtaaagta gcctatttct aggtggttag gcttgaaaag atagactgaa aagataggam 300

attttgtatg ccttttttgca aattgtattt acttctaaga ccgatgctgt tttagcttaa 360

cttttaaaaa agtgttcttc aaataattgt aatattttac acgatcttga agttcttcaa 420

ataaacagag tttagaaact aaaaattata gtgggatttt ctggttttga aggcttggaa 480

tgtatgattc ttactaatag atgttttatt cttgtgattg aaaataaacc aaattatgac 540

atggaatata atattactct gggtaaagtt tgtgatatat atcttctgtg tgttttgta 599

<210> SEQ ID NO 143
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 143

gttaatcacc caacttttttt cctgttatta ttttatgatc ttttcccttt ttactactca 60

taatatttta atagaaattt ttttaatgtt aaaaaagatg aaaaaaataa gaacttctgt 120

cacaagttct ggtgttctgc attgctgtga agctgtgttt tttttttcct gggcaaaatt 180

atttaagatg acataaaaac ccaaagtcaa cctctaacat ctgtccttgg cccttatatg 240

tcattcctac tactatagta ttctcattgc agcgttattc ctttctctct gtgtgtcagy 300

tgaagaacca tcatttaaac acttgcagtt tgaccctcat tatgtacttt gtttcaacac 360

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atggagatgc ccagcttact agaggctgat aatctgaagc agcagtgacc cctctaacca 420

caacatctgg aaaacaaagg ttgcataatc tggctagtct ccagaaattt tcagttatta 480

aaatctgact ttgtttaaca gcaataactc aatttattga atggattgca agagatatga 540

atcaatggct atatatacca ttcaaattta actgcaaaga attcacattt ttgaaacaa 599

<210> SEQ ID NO 144
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 144

aaactgctaa caaatatcat tcaactgctt aaaccccatc catgatgctt catgagtcct 60

ggacagtcct tagtatgata tgtgagatcc ttcatgatct gccctccctc gaactctcca 120

cactcagttt tatccaccag agcataatca ttctaaattc tttctgtatg gaaatattta 180

gttttccaga tatgtctcct ttatttttt gcacatactg gcctctctat aatcttcatc 240

tccaaaccag gccaattcca atgtggtttt caagagacag cccattcttt gcctctttgr 300

gaaaccttac cctgtgtctt tcctcccagc aaacaaacaa ctaggtgttc atcctttgtg 360

cttccagaga atcttctgta tatctctaca gtggtatagc attcagatag tttattgttt 420

tatagtgctc ttcctcacta actaaactaa gaggtttttt ttagaatagt tcctgaacgt 480

tagatttctg tattatgtgg cacaattcag aacatacaat gggtatttaa taaattcagt 540

gggtttttt ccttggaatg tgttggttaa ataaataaac tatggtcatt tctggagat 599

<210> SEQ ID NO 145
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 145

gctaacacat atcaaatatt tagtatgata catagtacca tgggatatgc cagacactgt 60

taactactta ataaatatta cctaatttaa tcttcataag gcctgtataa ggaaggcaat 120

gttacctccc ccactttaaa gatcaaagag actgaggcaa agaatgataa aacatcttgt 180

cctaagtcat gaattagtga ttaataaagt caggaataaa acctaggaag gttgctccag 240

agccttcact cttagccagt caatctcctg actcctatgc tattaatatg cataaacccw 300

tttccatgca cagaactagg tacataataa gggcttaata aatgttggat aatactattt 360

ttatactttc tcatgtggac aaagaaaggg atgcctaata ttgactaaag gtttactcta 420

agcataaggt attctcttta caactaacct ggaaggcaca cagaggccca gggaggttcc 480

atggctcaac cacagtcaga agccagtaag gacacaacca ggattcagaa gacattggtc 540

ttggtccaaa gcccatggtc ttattactac attccaacat gaactcttat ttggatcaa 599

<210> SEQ ID NO 146
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 146

tttttcttgg ctgaataata ttccattgtg tatgtggtgt gtatgtatgt gtatatactt 60

acatacatat gtatacatat acacacacac atacatacac accacatttt cttttctatt 120

catctgttga caggcactta ggctgtttcc atatcttgtc tatagagaat aatgctgaag 180

caaatattgg agtgcagata tctctttgac acacaaattt cattcctttt ggatatatac 240

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ctagacgtgg gattgctgga tcatatggta gttctatttt aatttttga ggaaacctcm 300

tactcttttc tacaatgtct gtagcaattt acattcccac caacaatata aagagaatgg 360

gtttcttttc tccactttct caccaacact tattatcttt tgacttttg ataataatct 420

tcctatcagg agtaagatga tatctcattt tggttttgat ttatatgccc ctgatgatta 480

gggtattagt cagggttctc tagagggaca gaactaacag gatagatgca tatataaagg 540

agagtctatt aaggtgtatt gacccacatg atcataaaag ttccacaatc tgctgtctg 599

<210> SEQ ID NO 147
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 147

ttttctattc atctgttgac aggcacttag gctgtttcca tatcttgtct atagagaata 60

atgctgaagc aaatattgga gtgcagatat ctctttgaca cacaaatttc attccttttg 120

gatatatacc tagacgtggg attgctggat catatggtag ttctatttta atttttgag 180

gaaacctcat actcttttct acaatgtctg tagcaattta cattcccacc aacaatataa 240

agagaatggg tttcttttct ccactttctc accaacactt attatctttt gacttttgr 300

taataatctt cctatcagga gtaagatgat atctcatttt ggttttgatt tatatgcccc 360

tgatgattag ggtattagtc agggttctct agagggacag aactaacagg atagatgcat 420

atataaagga gagtctatta aggtgtattg acccacatga tcataaaagt tccacaatct 480

gctgtctgca agctgaggag caaggaagcc agtctgaatc ccaaaacctc aaaagcaggg 540

aagccaacag tgcagccttc agtttgtggt cgaaggtcca agagtccaaa agctgaaga 599

<210> SEQ ID NO 148
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 148

gtgaggactt tctggcactt cagataggaa aataggggta caaatactat gattatattc 60

aataaacaaa atggtttatt tcaatggtgg gtccctgaca cattctgaaa ttttgctctc 120

caatactaac ttttgaaggt ttaaaaagtc actaaatatg acaaaattat gttgatttaa 180

aatatttctt ctttgattct ggggtcattt gctccatttt ctacagcttc aaaaccacaa 240

atataagtga gtagaaatat ttaatgcttt ttagtttttt gtctattttc tataaatatm 300

ttgagactgg cctgattata cagtctaagg aaggaaaacg gtgtcagagc aaatcttcat 360

tttattaata aaaatctaag aaataagagg aagtaagaaa tgttgcttca agtaaaacag 420

aaataaaaac caagcaacta aaaacaacaa aaaagaacat attttcatga aaaataaact 480

ggtgatgtgg gagcagaaaa gagaaggaaa ataatcttga aataaccttt taaagtcaga 540

tgtattcaac tcatcagaac aaggaaaaga tgacaataaa agtttagaga gttgattac 599

<210> SEQ ID NO 149
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 149

gcaagttatg ggaacctctt tgcactttac attactcatc tgtgcagaga attatggcat 60

ctttcctgtt gttattgagt tgttggaaga aaaaatatga cagtgctttg taataataaa 120

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acttatacat ataaggggat tgtaataatt aaaattcata aagaaaatgg ttgatgagat 180

cgcccagcca ctgttatctt tgaggactca tgaaagcaat agttggaaat aatttctctc 240

tcttgattag acacactgtg gagttagtgt tgcacccagt ttttgtctcc ttaccttaay 300

aaggatgctg tgaagttaag gagtttggag tagattaata atatgattaa agtgttgaat 360

aaataagacc catgagaaaa ggagtttgaa ttaattagtc tggaaataat aactgccttc 420

taatacatga agcattatta caagaaaaat atagaccatt tctcttctct gagaaatgac 480

ttgaaagtaa ctgtggacat ataacacaga cataagaagg aattcactga tagggttgag 540

agttaaatat taaaacagga tataagaaga atatttggca tctcctttgc tgctaacta 599

<210> SEQ ID NO 150
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 150

ggcttctgcc attttgaaga aaaatctggc aaagtcattg tgcatatatc atatgattat 60

ctgatctcac tcttaaagag aaagggggag ataaaaattt tataaaagaa tgtaagataa 120

tatgtttttt cacaacattg tttatgaagg cagggaactg gaagcaacat tgttgtccat 180

tattagagga ctatactaaa ataaggttgt ggaggcatac tactgaatac cacatggtag 240

ttagaaacaa catagatctt aaaagtgtaa tgctttgtga aaaacagaag aaaatgaatr 300

ggttccattt atgtaaattt aaaagtatac acaaaaaaat gacactacat gtttctaaag 360

atacatataa atttgagaat gtatatcaaa cacattagag cagttacctg tttgggaggg 420

agtagaatat gataacaaga agaaatcagt ttaaaattgc ttttttttt tttgctttgc 480

tcaaatcaat gatgataatg tgccatgaac cagagtctgc atctatctca ctctcctctc 540

tttttcttta aaaaaaaaaa aaaaaaagga aagaaagcta catacattgt aaaatagta 599

<210> SEQ ID NO 151
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 151

gtcatttttt tgtgtatact tttaaattta cataaatgga acccattcat tttcttctgt 60

ttttcacaaa gcattacact tttaagatct atgttgtttc taactaccat gtggtattca 120

gtagtatgcc tccacaacct tattttagta tagtcctcta ataatggaca acaatgttgc 180

ttccagttcc ctgccttcat aaacaatgtt gtgaaaaaac atattatctt acattctttt 240

ataaaatttt tatctccccc tttctcttta agagtgagat cagataatca tatgatatay 300

gcacaatgac tttgccagat ttttcttcaa aatggcagaa gccaaatatg aagaaatact 360

catttatcca ttaacaatta atattatcaa aatcagcaat ttttttcccat atgatggatg 420

taaagtagta tctcattgtt aaatttattt tctatttact gagataatat actaattatc 480

catatatttt ccatctttct aggtttttag tcttgctgat tctaggagtt tcttccatag 540

taccttttatc attccttttgt ctgtttctta tgtctgttca attcatctat ttgtctatt 599

<210> SEQ ID NO 152
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 152

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aaaaaccttg gaatatgctt ggcttttcta ttgtcttgtc catcagtaaa atctaacttg 60

tctattgcca caattctagt tcaagtcatc attatctttt gcctatactc tcctaattgg 120

tgtccctggt tctgcttttg tctctctaca ggatacttta tagcagccca ggtgatttat 180

ctaaaacata attttaataa tatctgcttt aagttttcca agggcttcct acttcactct 240

caataaaaat aaaaatcctt gccttgactt ccaataaatg atctggtccc acgccaccty 300

tcttacctcc ttttctaaca ggcttccctt cccatcctac ctctcaactc cacttcagta 360

gcactaggct tcttgttcct tgaacagaga aagcatactt ctaatttagg ggctttatca 420

cctgcagctc cctccatctg gaatgctctt atttcagatt tttgtacggc ttagttcctc 480

actttttca gggttctgct tgaatatcat cttatcttga ggacattccc ttaacactct 540

ttaactcaca ggcaaagatg gagaatcaaa catgtgcatt tcccttagca ccctcttca 599

<210> SEQ ID NO 153
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 153

atggcagtta atgattgtat tttaagccta taaactcaca aagacaaaaa gaacaaagaa 60

gactctaatg acaaaatttt ggaaggtgga gagaagagat aacaaaacac acacacatac 120

acaacacaca cacacacaca cacacacacc atgactatcc attcctctta cctagcttta 180

tttttcttaa tagcacttca cctagataaa tgtaagtaaa tataaacaca agatatatat 240

tgatttttac atttgtttgt tgtcgcttcc tttttgcttc cagaacataa gctgcatgay 300

agcaatcttt tcagttttgt tttggtgttg cattctcaag ctttggaatc atagcagaat 360

caaattcagt ataaattttt gactgaataa ctgaggtgga ctggatgagt gtagtttgtg 420

tgaggtgtgg ggttgtggga atcaagtgtt caattttgaa tgttaacttg aggtgtctat 480

tagacatcta agtgatgata tcaagtgaaa tccgcatatc tgaggctaag tcatggctaa 540

aattataaat tttagagtca tcaacattgg ctctaaagaa gatcacctgg ggggactat 599

<210> SEQ ID NO 154
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 154

agccaagctc caagccttgg aggacaacac catttagaga tcaggcagag cagaggtctt 60

tgaaccttat aattatacac tacaatttgt aagaagaaga aaaactaatt taaactaagc 120

aatgtgatat gtagatattt atctataaat aatatatatg tatctttgca caaatatatt 180

atgtacatta caaaatacac agacacagat attaaaaaag aatgagctga acaacttcca 240

gttaaagagg aagtattgaa cacatgcatt tttcagctcc ctgctaaagg cccactacar 300

tgatagtaaa tggattttaa aaaataaggt ataaacccac aaggacaaag agaacagcag 360

acaaacaata ccaccaaaat ataggaagct gtaaagaaga aagacaaata acaactgact 420

cacagactca ggaaagctga ggctgcagtg gagaaaaagc agagatacaa cctgatttac 480

aatacagaat cagccatgcc cctgcccccc tgcaaaggct cagaaattgt ttctggcact 540

tctgctagtg gaggttaatg ttgggcaata atagacttag ctgaatgtct gtttgagaa 599

<210> SEQ ID NO 155
<211> LENGTH: 599
<212> TYPE: DNA

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 155

catgcccctg ccccttgca aaggctcaga aattgtttct ggcacttctg ctagtggagg 60

ttaatgttgg gcaataatag acttagctga atgtctgttt gagaagcaga tacatccaca 120

gacaccccca ccactctaca ctaccaagtg actaacctct accaggcagc aacagcctgg 180

agacttattt tctgaagagg gttaagaggg gatcttgctt gcagaacaac aggcacacgt 240

gaatgggaat tccaagtgga aagcagggag attaagtcaa agttaatatc agaatgcttr 300

aaaccaaaat attaagaata atttctattt gttactaagg gatgtggagg caaataaaaa 360

gaacactatt ttgttgtgta gcaatgattg ccaatggaat tcacctacat aaaaagaatt 420

ttaaaataat gaactgctat ataacatttt ctttatttct tagagctatt tcaaatattt 480

atttctattt cttttaaagt gcatggattg tttgaacatt atcttggtac atgaatgcag 540

gcattttaaa gtaattgcat ttgttgtatc ctggattaga agcaggcata aatattgat 599

<210> SEQ ID NO 156
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 156

atgccatgaa tgtgattgtg gttacactct atgcccaatt gtccaaattc agtgaagtat 60

gcacttaagc ttgatgaatt ttatttatgt aaattatact ataataaaac tcacaaaaat 120

gtttaacaga gagaaaacaa acagtgggag aaaaaatcct ttcagtacca ctacatttct 180

catagtaaag ttggctaagt catatcagtc atatgtgtgt gggcaagagg agggttgtcc 240

caaggcaatg ggtgttgaac agaggaaata ggggactttc tgaaatgtcc atagaggagy 300

gacaaaagga gtaacctggt tcagggagta gaggaagggt aactaaggaa cagctgaggg 360

tgtggggcca tttcgaacaa aactctttca ttatttacat ggtccttcat gatctgggcc 420

ttgcctgtgt ctccaactca cttgcctacc ctctctctca gtctgttttt actctgactt 480

cttgtttagc tctttcttaa gtttctttgt gcactcctca tagctctatg ctgggccctg 540

ctttttttt ttttttttt ttccacttac acccttgtt ctctttaggt caattatcc 599

<210> SEQ ID NO 157
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 157

tgagaagtaa gtaacaaaaa aactataatc cttaaaaaaa tcagttgaat taacaaaggc 60

acttgcttca cacaagatta aattaggcca tatgaaaagt tactttgcat aatctcttca 120

tgactttgca tctagttatt tccaagctaa tatatctagc ctctaattca aaaagaattg 180

tagacatgac tttattatct tccttatgga aaatttcttg ataaaaatta ggttgcttca 240

ctattgattt gaatctaatt ttagcagtgg ttagaagttc caacacagct ttctacaagk 300

atttgagatt tgacatccat cttagtaggt gttgatttac tttctgtttt aagcagtttc 360

cacattaggg atttggggct cattctaccc acaaacccta ataattgcct aggtataatg 420

ctactctgca tatatcacat gactggtgga aaaataaatc attcatttaa caaatattga 480

tcaaagttct gctgtgtgcc aactattatg gcaagtgtgg aagaatcaga attaactaag 540

aagaaaaaac agacatggaa acatttcaag gaagaactag ctagaaggga aggatacag 599

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<210> SEQ ID NO 158
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 158

ctcctttaaa aaaattggaa ctgtattttc atcagtgaaa ccctctgctt taaaatctca 60

gtgtcattgc caaagactaa atacattgac cttggactca attttgagct acacattcat 120

ttctctagaa tgttggtaaa agttgcagaa gtagagtcat ctgtatattt ctcttcaagt 180

ccttaaactt ttagtaaacc attatttatg gatctaacac acttgtaaac aatgccagca 240

acatattatt tgtcctgcat gcttataaaa ttctttttt ttttttggt catggttagr 300

tgattcccgg taactacatt ttaattctaa ttctgagaag taagtaacaa aaaaactata 360

atccttaaaa aaatcagttg aattaacaaa ggcacttgct tcacacaaga ttaaattagg 420

ccatatgaaa agttactttg cataatctct tcatgacttt gcatctagtt atttccaagc 480

taatatatct agcctctaat tcaaaaagaa ttgtagacat gactttatta tcttccttat 540

ggaaaatttc ttgataaaaa ttaggttgct tcactattga tttgaatcta attttagca 599

<210> SEQ ID NO 159
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 159

ttttctggtt tcttctcatt tgctaaagga aggcctaggg ctcaaggcta ttgtttagat 60

tcttttgtcc catgggttgt tcccttgagg tagtagtctc tccctttcc tagggaggtg 120

gcttcctgag agccaagctg tagtgattgt tatctctctt ctggacctag ccacccagca 180

agtgtacaag gctccaggct ggtcctgggg gttgtctgca cagagtcctg tgatatgaac 240

tgtctgtggg tctctcagcc gtggatacca gcacttgctt cagtgaaggt ggcagggggr 300

tgaaatggac tctgtgagaa tccttatatt tggttggtta atgcactatt tttgtgctat 360

ttggcctcct gccaggaggt ggcggtttca agagagggtc agctatggta gtatggggag 420

gaacaggtgg tgggcagggc cctagaactc tcaagagtat atgtcctttg tcttcagtta 480

ccagggtggg taaaaggacc attaagtggg ggcaggtcta ggcatgtctg agctcagact 540

ctacttggac aggtcttgct gcagctgctg tgggggatga aggtgaggtt cccaggtca 599

<210> SEQ ID NO 160
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 160

gtaagttatg ccactgtcct ctgagtgaag gaaacacagt agtgcctttc catcatgtat 60

ccaagaagaa ttatgaacaa attcttgggg taggctgagc atcttaacag tggcaacagc 120

agaggtgtac agggtgtccc cacactcact tccagaactt ggtcatctca atttaccagc 180

ggttcttatt taggttctca tagcccagaa aattctgcca gggtactaca catagtgggc 240

tatttttagc actgggcctg cctcaggaaa ctggagaact tgaacactca ttgacaaggr 300

agtagaagac agcaaagact taagagagaa agatgagatg ctttatattt tcctcctgtg 360

attttatttg gcagctcatc atccagttag gaaggtctaa gagataacga agatataaag 420

tgctgagtag agagatacac acttgggaac aggaaagata gctggcagtg ggaaggagtg 480

-continued

tgaaacattt tttacatgga gaggaggaaa agctgtggaa ttgggttact taaacataga 540

gagggagtta agagcaaaga ggctctttct ggagaagttg atcaagacct gaagtgaaa 599

<210> SEQ ID NO 161
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 161

catgtatcca agaagaatta tgaacaaatt cttggggtag gctgagcatc ttaacagtgg 60

caacagcaga ggtgtacagg gtgtccccac actcacttcc agaacttggt catctcaatt 120

taccagcggt tcttatttag gttctcatag cccagaaaat tctgccaggg tactacacat 180

agtgggctat ttttagcact gggcctgcct caggaaactg gagaacttga acactcattg 240

acaaggaagt agaagacagc aaagacttaa gagagaaaga tgagatgctt tatattttcy 300

tcctgtgatt ttatttggca gctcatcatc cagttaggaa ggtctaagag ataacgaaga 360

tataaagtgc tgagtagaga gatacacact tgggaacagg aaagatagct ggcagtggga 420

aggagtgtga aacatttttt acatggagag gaggaaaagc tgtggaattg ggttacttaa 480

acatagagag ggagttaaga gcaaagaggc tctttctgga gaagttgatc aagacctgaa 540

gtgaaaatct ttaaaagttc tgaaagagtg gctaaaaaat aattgtaaat tacttacga 599

<210> SEQ ID NO 162
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 162

tagtgcataa ggcctccagt tgatatgtag caagaattat taattaaact tcaaaacaag 60

aacatgtaaa attaatatta gaaagataat tgtgtgttct aagcaaaaga aaataactca 120

caggaggtac tgctgcactg tccacaattt tagactacat gacttctaaa atccttttaa 180

ctctcagtaa aaaaaagtag cattatcatt cctttgtatc aaaaaacacc atagatgtta 240

tctcttttaa tgttgccttt tcttcaactt gatttttttt tcatttggtt ttccagtgar 300

aagcaattga tactggaagt cttggaatat ggcatttcat aatttgcata acaaatatca 360

gctctgctct tcaagaagac tgaagttttt ttggttttat agtattttat aaaattttat 420

aatttgtact taaaaaattg tcagcaactt tcatttaaac atcttatttt aaattcttcc 480

agttatctac agacacacac acacacacac tccttctcaa tgcaatctag aaaggagcaa 540

atgtacaaga ttttttgtct ccactatttt ttctttttcc ttgcaacaat atccccatt 599

<210> SEQ ID NO 163
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 163

aatcatgaac gaaactgttt taatccacca ataataatga atttcaatta cccatgtttt 60

ggagtaaaat cgaattatct ttctattctc tttacaggaa aaaattataa ttataaaagt 120

attgtcatgt taggaggtgg taaaacagta tgtaacccaa aacagagaaa aatggtatta 180

tagaaatggg tcaggtagtt aagaaataaa aacatcagca ctttcctgtg ttttgtggtg 240

tttgcaatat ttgtgagctt tgtaacattc gacttgtgat ttttttcctt ctcattctar 300

taaatattca ggttggtgtc tagttttgta gttgcaattt tgtcttcttt ttctttttct 360

-continued

tttcttttct ttttcttttt ctttcttctt ttttttttct ttttgagaga gagtctcgct 420

ctgttaccca ggctggagtg cagtggcgcg atctcggctc actgcaacct ccgcctcccg 480

ggttcaagta attctcctgc ctcagtctcc taagtagctg ggattacagg cgtgtgccgc 540

cacgtctggc taattgtttt tgtatgttta gtagggacag ggtttcacct tgttggtca 599

<210> SEQ ID NO 164
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 164

tcccttgggg ctttccccat agtgagcatg tgatgctttc aggggaacac tgccttttaa 60

tttttatccc aagattcaag cagcacagat cctctcttgc ttcacagccc ctgtccaatc 120

ctgcctttca ttaactaact ttagtaactt tcctcgctgt gtttaattaa gattcatacg 180

agcaagactt gaaggaacac aagcatctca gtgcggctgg gccggccttt agtcttgggc 240

tttttacctc ttgcccgtgg tggtgctggc tgcagaggac cccctgagct gggagtagam 300

ataactcacc ttggtttttt tcttgctgcc agacttttag gatggctctg aaacaccaga 360

ctaagtctgt gtccaaaagc ctcaagcatt ggcctgggat tatgtaggtg gatatcattt 420

gaggactatg gaggccaaat tatttccttg attgtctaat ctccttgtta acaacatttg 480

tgaaaaaatg aagggttttt tttttttttg ttttttgttt ttttggctg caatggaagt 540

ttcaagactt acaaggaaac agcttttgct gttcccctct tagggccttc cagcctgac 599

<210> SEQ ID NO 165
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 165

tgggattatg taggtggata tcatttgagg actatggagg ccaaattatt tccttgattg 60

tctaatctcc ttgttaacaa catttgtgaa aaaatgaagg gttttttttt tttttgtttt 120

ttgttttttt tggctgcaat ggaagtttca agacttacaa ggaaacagct tttgctgttc 180

ccctcttagg gccttccagc ctgacaaaag aaatcagcag cttgcccgtg ggcaatctgg 240

agaggcagga aggtgggtga gggaagcatg acatcatatc aggtgggaat aaaaaggcgy 300

gtcctgcagt gtccctgttc aaacatattt tggtgcttgg atgcccgctt tggaagctgg 360

aagaccctca gcaggaactg cgaagggctc cagagacccg gactcaagtt ttcaaacttt 420

aaaaatgagt atggcaaggg aggagtgagg ggtgaagggc agcagccccc tggtggggag 480

caggggcgcc gggagtcaga tctgacagag ggctcccggc tgtgtgctgc atgcgtggtt 540

ccccttttc ttggagaaaa tggggaggca ggagtgaggc agattgctct gggacaatg 599

<210> SEQ ID NO 166
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 166

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atcatctgtc tcgcaatctg ttttgaaggg gaaagaaaga gcgggcagag aggagagagt 120

cgttttctac taggggaggc ttcattcaga gagttttata ggagaagaca gatgtcatga 180

atactgatgt ggagagcctg ggtctggcag agtttttta attttctgag ttgtaaagac 240

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aaagtgtttt aataacacag ggaaacacat gttgatgggt gggtctttag ctcattctgr 300

tttctctaac tccctctctt tctcctcctt tctttccgtc tttctgcctg cctgcctgcc 360

tgcctgcctg cctgcctgcc ttccttcctt ccttccttcc ttccttcctt ccttccttcc 420

ttccttcctt ccttccttcc ttcctccctc cctccctccc tccctccctc ccttccttcc 480

ttttttgag acagggtctc gctctgtggt ccaggctgga gtgcaggggt gcaatctctg 540

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<210> SEQ ID NO 167
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 167

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gctaagcctg cccttggaca gataagaaaa ctgcagcccc aggcacagag gcacaagctg 180

agaggtgacg tcaggactga actgtgagcc tgggagtcca aatctaggct cacccagtct 240

ttctggctcc agtgagggcc cgccactgtc atccgacgga tggcatgtgt gatttttggy 300

acacgcctgt gcaggtgact cccacaggtg ccccggaggg aggcgctgct gtgatgttca 360

tgctacatgc aggaaacaga gaggttgagt gacttgccca cagccccaca gctcctacct 420

agtgaagcct ggtttgaggc cacacctgcc ttactagttt tattatttat ttatttttg 480

agactgagtt tcactctgct gcccaggctg gagtgcagtg gcgcagtctc ggctcactgc 540

agcctccgcc tccggggttc aagagattct gctgcctcag cctccagagt agctgggac 599

<210> SEQ ID NO 168
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 168

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ttcatgtctg gcttatctca cccagcaaat gtcgtctagc ttcatctgtg ttgtagtgtg 120

tgtctgagct tccttccttc ttaaggctca atactattcc aatgtgtgaa gagaccacat 180

ttcgtttatc tgttcatctg tttggtgact gagctccctc catgctctcc aacaataatc 240

atgctcctcc acagacaggt gtcttggctg atggtgtcag agacccccctg gcaagccgcy 300

gctatgggag gggtcttctc cctctcatgc cacccaagga gactctgtgg ggtccctgca 360

gaccccgcag catggtcagg ggctctgact ggaggctgtt ccctccaaca ggactcagca 420

gtcagggtct cccagggaac ccctgtatgc agactctggg aagacaggtg gatcaggtgt 480

ggggactgtc tgtccctcag gagctgctgg ttgaatgaat gcgactgtct cctgctggga 540

cacgcctctg cctcaggctc tgggcagtgg gggacgtgtg cccctaaaga aggtacaac 599

<210> SEQ ID NO 169
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 169

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cacgtacata gtggatgtgc ctctttttcg gggcaggggg taatcttaat caccaagcaa 120

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ttactaaatg ccgaccatgt tctcaggctt ggcagaggtg ggtgcttgtt accccaaggg 180

acaaccactt ccctccatgc tccccacccc acccaagacc cttctccact ccactcctga 240

ctgccgcctc ccacctctgc cctgggtcgc tgtctttatt gtcttcctca acatcttccr 300

tgggaaaggc caatggcttg aaacaggatt gacgagacac ccggggcctg ctccacaccc 360

gtgggctcct gggcgtgcac ccaagagcct ccacccctga atggctggca tccaggtggg 420

cttcccataa ggagcccccc tctgcgggcc tgggagggtg gggagcctgt ggcgaggtgg 480

cggggaagag aaagggcaca ggtgcccccc cactccgagc ctatcggatc ccggagactt 540

gcaggctata gacctagagg tccagccagg agggctggca gggaccatga agcaggaga 599

<210> SEQ ID NO 170
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 170

cccctcactc cgagcctatc ggatcccgga gacttgcagg ctatagacct agaggtccag 60

ccaggagggc tggcagggac catgaagcag gagacgtcag ggcagagaga atgcctttta 120

gagccagata aattcttact tccccctttcc cagctgcgtg accctgggaa acttcaacac 180

tccgtgtctc agtcctctca tctgtaaaat gaatctgatg agaactgtgt aagaatagag 240

gtgtgtggag agctctctgg tgccaggctc atggcaagac tgtggtgaca ccagccatcr 300

gaaggcaggg aggctcctct gtggacagct ggatgcacag gtgcgtagca ggagctcagg 360

agggtgtgcc cgcggagtcg caggtaaggg agccactcca gattgcagag cttggcttgg 420

aggtgtcgcc tcaggagggt cttccattgc ctggagaccc cacataggcc ctcttcttcc 480

ttcaaacaca gcccccaacc tctctgcagg gaagtcctcc ctgaccttcc aaaccagggc 540

agacccttgt ctgggctccg tcggcctgga catggtgcca tttcccacta gtggggcag 599

<210> SEQ ID NO 171
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 171

ttgctctcca aggttcctgg actttcctcc agacccgagt gcaagctccc tgtggcttcc 60

acccaccgct cacaggagtc tctgcagcca ccagacccag agcccagaca ccatccactg 120

tcggggagag gcacgtgtcc acagcttcct ggaatgcaag gctgcatgtg gccagggctg 180

ctgcccgctg aggggcaagt gcatgcctgg agaccacagt aaggagccag tctcatgctc 240

tgggagttta gataaggctt catgcccctt ggagccaaac ctctgaattc catggagttr 300

ttgggtcaaa gagcttgcct aggtctgagt tgtggatacc tgttgtcaat gagctctcca 360

caaaggggtt accatgatag gtcccaccac ctgtacctct cctctccaaa tttcaccact 420

gttctttcac acctttgcca atttggtaag tgcaaaatga tattttagtt gtctatgctt 480

acactgattg gaggaatgct ttaagtttga ttattggtaa gtgaaacatt ttgttacctg 540

tatttactga tcccactttc cttttatgaa tgtcccagtt acatcttttg tccatttttt 599

<210> SEQ ID NO 172
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 172

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ctggtgacat ctctgctctc atctcccttc ctctccctgg tgtggacact gcacccacca 60

ccagctctga gcacatggcc cattggctct gcaggggccc tcctctctgt ctgcagtggc 120

caccttgcca ccaggcccac ctgaaggaac cgtgcctctc tttacggact gaccccaagg 180

tttgcccatg cttggaggtc tgtctgactt tgctttcctg atgcctggca gtggaccacc 240

atgcccactt gtcggtggct gtgtagctca tactcactcc atctggcagt ttccacccam 300

cgaggaccac tcaagtttgc cccactccat gtctgctgtt gggaggggat ggtgcatccc 360

acaagcaaca ggagccacgg agctgggggc tggggctgtc agcctggatg ggccaggagg 420

ggaccttgct gtgcctagtg gaagagtagg tggtccccta ctggctccag gccgctgggt 480

gggtcacttg cccatccctg cctgggtgtc tatagtgggt gttcccgcca aaattcatgt 540

ccccctggaa cctcagaatg taaccttatt tgaaaatagg gtctttgcag atatagtta 599

<210> SEQ ID NO 173
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 173

cgaggaccac tcaagtttgc cccactccat gtctgctgtt gggaggggat ggtgcatccc 60

acaagcaaca ggagccacgg agctgggggc tggggctgtc agcctggatg ggccaggagg 120

ggaccttgct gtgcctagtg gaagagtagg tggtccccta ctggctccag gccgctgggt 180

gggtcacttg cccatccctg cctgggtgtc tatagtgggt gttcccgcca aaattcatgt 240

ccccctggaa cctcagaatg taaccttatt tgaaaatagg gtctttgcag atatagttar 300

gtaaggatct tgagatgtgg tcatcctata ttgggggagg ggacagtaaa tacaataaat 360

gtccttggga aagacaaaag aaaagaccca gccacaaaga agaaggccat gtggagacag 420

aggcagggat gggggtgatg tggctacaag gcgtggaact cagagccccc agaagctgaa 480

ggaggcggga agtttcctcc caagagctgc caggggtggg gcggggcaga ggtggcatgc 540

ggaatgctct gcccacactg gatgtatgaa tctgttctca tgctgctagt aaagacata 599

<210> SEQ ID NO 174
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 174

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agtgggtgtt cccgccaaaa ttcatgtccc cctggaacct cagaatgtaa ccttatttga 120

aaatagggtc tttgcagata tagttaagta aggatcttga gatgtggtca tcctatattg 180

ggggagggga cagtaaatac aataaatgtc cttgggaaag acaaaagaaa agacccagcc 240

acaaagaaga aggccatgtg gagacagagg cagggatggg ggtgatgtgg ctacaaggcr 300

tggaactcag agcccccaga agctgaagga ggcgggaagt ttcctcccaa gagctgccag 360

gggtggggcg gggcagaggt ggcatgcgga atgctctgcc cacactggat gtatgaatct 420

gttctcatgc tgctagtaaa gacatacctg agactgggta atttataaag aaaaagaggt 480

ttaatggact cactgtccca cggggctgga gaggccttat aatcatggtg gaaggcaaag 540

gagatgcaaa gtcgtgtctt acgtggcggc aggcaagtga gagagagcat gtgcagggg 599

<210> SEQ ID NO 175
<211> LENGTH: 599
<212> TYPE: DNA

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 175

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gtgtgtcttg gagtagccca tgtcatattc agaatcacag ctggggctcc aaatcccact 120

ggcctaccca ttaatctatc actgtagact agtggtagaa ttggtgacca gatattctag 180

tctgggatat gatcttggga tcttaagaga actttctgca cttcaaggtc cagtttcttc 240

acccagagaa ggggctgcca ggtataccac gagatgagag ttcctccaca gggggacacr 300

attgcagcag agatggccaa gggcaggaac tcctactatc ctcatttata tatgaggcaa 360

acaagacttg gagaattcaa gtgacttgct caaggtaatg cagccagcct caaagaaagg 420

gagccgagat taaaaccctg gcccacatgc tccagagctg ggaggctttt ctgtaggccc 480

atcaggagat aagttatgtc tcctggctga aggccacctt ccacctccca gcccccaagc 540

caattgcatc agacataaag atttgtttca gggtgtcttg ttggttttcc agctccaac 599

<210> SEQ ID NO 176
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 176

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tctgacaaca cccactcctg ctgccacagt ctgtcctttc tgctctgggg ttctctgctg 120

cagtgccttt gggagcttct cagccatctg actcatgctg gcgaggtgtg cactctgcag 180

cagcgccagc tgtaagacac accctcagat gggcttgtcc tcttgccctg tttcatgcct 240

cctggtccct gtttctgggc cttatcccca aaacgtgaca cttgagtaag ccctttctm 300

aggctcaggc agatccaaaa gcacatttaa atattttcag gattctgccg atttagagca 360

actaggattc caaagaagga aaacttactc aatcagttta ttgtcagagg ctccacatca 420

ttcatttgtt tattcatttt ttcgcttatt cattcagtca ggccacaagt ttcttcagga 480

ctgggatcat gcttgtcccc attctgttcc taatggaggc tatccatgta gtagtcgctg 540

gcaaataact cttagtgact taagttcagg aggcagaagc atggtgaagg gggcagata 599

<210> SEQ ID NO 177
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 177

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ttggaggcgt gggcccccaa gcatgtcccg tcctgcagac actccctgct gcccgggctg 120

accatggggg catcctgcct ggtgccagcc agcccagcct tgtctagcct gcctctgcca 180

agtggcccat ttgactgtcc ccatctgttt gcccatggag tccggagggt gtgccctggc 240

ccagagccca gctgcagcct gggaaacacc agactccatc catggctctt tgttttatay 300

tttatccaat aggcagtaag gacctcagag agcatcaggt ccagacctct tgccctgcac 360

aaatggagaa actgaggcag agagagggaa ggggcaggtc agaggcagta tggggttgag 420

tcctgcgctc tttcaagatt ctgttggcta aatccattgt ccccagaagc ccttgtgcat 480

gtagttttcc atgccgtgat gggggctggg gagtcccttg gcatcaaatg ggtggtttgg 540

attctgctga ggggtccacc tgcctggtga gcaagagacc aggagccagg agccaggag 599

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<210> SEQ ID NO 178
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 178

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atggttcttg ctatatgaaa ctgccaaact ttttcagagt ggctgtacca ttttacagtc 120

tcaccagcaa tgtaggagtg acccagtttc ttcacatcct caccagcact tgataccatt 180

atttttatt ttagccattc tgataggtgt ctagtgatac ctcattgtag tttgaatgtg 240

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tctttggcag agcagaattt ttatttggat taagtccagt ttatcaagtt ttccttttat 540

ggatcggctc tgagagtcaa gtctaaggac tctttgtcta cttctagatg ctgaagatt 599

<210> SEQ ID NO 179
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 179

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tttattgcaa atggatatcc agttgcttca gcaccatttt ctataaatgc tatttttctc 120

catcgaattg attttatacc tttgttaaaa attagtgggg tgtattcttg tgaatctatt 180

tctgggttct ctgtactgtt ccattgttct gtatgtttat ttgtctgcca ataccatgaa 240

cttttgatta ttgtattatt atttgattat ataagcctat atattaagct taaaatcaas 300

tagactaaat gctctcactt tattcttatt tttcaaaatt gttttagcta ttctaaaacc 360

ttttcttttc tatatacatt ttagaataat cttgtgtata tctacaaaaa aatcttactg 420

aaactttgac aggaattgct gtatatcaac catacctaaa cactgattta gggaggattg 480

tcatctttac tatgttgggt cttctaatct atgaacatgg tatgtctctt catttattta 540

gattttcttt gatgtctttc atagtggttg tgtagttttc agcatgcaag ttctgtata 599

<210> SEQ ID NO 180
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 180

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atatcaaaaa aatttacatc tagttattta atttttgagt gatttcaata gcattgtatt 120

tttaattttt atgttcacat gtttactact aatacataga aatacaatca gttttgtata 180

tttatcttgt ctgtcacctt gctgaactaa cttattagtt tctgggaggt attgtttatg 240

tagattcatt gggattttcc acagcgataa tcatgttatc tattttattt ctcctttctm 300

atatgtatgg cttttgaatt catgttaatt attctgcaaa gaattggtac aattgtccag 360

taaaatcatc caggcttgga gatttctgaa atgatgtctt taatttcctt aatagttata 420

aggctatgca aattatctat ttcatattgg gtgagttgtg gttaagaagt tgatttatct 480

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aagttgtcaa atttatgtgt gtagagtggc tcatagtatt ctattttatc tttttgatgt 540

ctgcagggtc tgtaatgata ttcccggttt cattcttcat gttggcaatt tgcatcttc 599

<210> SEQ ID NO 181
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 181

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actccagaaa cttaaatatt agatttttg ttgtgtttct tgactcttgg ttccttttgt 120

tgtgtccctg aggctctgtt attttttatt tcagtctctt ttctctgtgt tgttcagatt 180

cagtaatttc tgttattctg tctcccactt cactctttcc tctgtccttt ccattcttct 240

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catttggttc ttcttatctt ctatttcatt gcaaaggctt tctatttttt atttgcttca 360

agtgtattca taattgatcc tggaagcatt ctgtcatggc tactttaatt attttcaggt 420

aactctaaca tctctgtcat cttggtgttg gcacctattg attgttgttt ttcatgcagc 480

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gtattattta gatcctgtgg ttcatctgga ttgtttttct tttgacattg ctttggcaa 599

<210> SEQ ID NO 182
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 182

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tcttggttcc ttttgttgtg tccctgaggc tctgttattt tttatttcag tctcttttct 120

ctgtgttgtt cagattcagt aatttctgtt attctgtctc ccacttcact ctttcctctg 180

tcctttccat tcttctgttc aaggtgtcag tgaatttttc atttctcata ctgtattttt 240

cagttctaaa attttccatt tggttcttct tatcttctat ttcattgcaa aggctttctr 300

ttttttattt gcttcaagtg tattcataat tgatcctgga agcattctgt catggctact 360

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aaactgggat gtttctgtat tatttagatc ctgtggttca tctggattgt ttttcttttg 540

acattgcttt ggcaagagaa gggggtctgc tgcctcatta ttgataggtg gaggtaaaa 599

<210> SEQ ID NO 183
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 183

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tcttaaatca gaagactgtg taggtgaggg tcagctctag actcattgct tcattgctag 120

tgtcaactat gggccaggat ccagggcttg gaaccaagaa cctctttgga ttaatgccta 180

ttaagataat attgaaaatg aagtaagtgc aatggagact catcattgca ttacagagac 240

agaaggggcc cccaaactaa tctggagtgg tgtacaggat cagggaagtt gccctgaagk 300

tgataagcag aatgtggaag gatgggcagg agttgtctaa gagaagagtg tggcaataga 360

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agggcaccct gggccacagg gaacaaacca tagctgaaag atgaggagtc aagaaatatt 420

ctggcaccca tggggtacta ttagcagttt aactttacag gagctgaaaa tttaagaagg 480

ggaatgtcaa gagatgaggc tgaaccttgg cagggatgga tccttggacc acatcatgta 540

gttgaccctg tcacatagct tggacttcac cttgtgggtg acaggaggcc accagggct 599

<210> SEQ ID NO 184
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 184

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ttacagagac agaaggggcc cccaaactaa tctggagtgg tgtacaggat cagggaagtt 120

gccctgaagt tgataagcag aatgtggaag gatgggcagg agttgtctaa gagaagagtg 180

tggcaataga agggcaccct gggccacagg gaacaaacca tagctgaaag atgaggagtc 240

aagaaatatt ctggcaccca tggggtacta ttagcagttt aactttacag gagctgaaar 300

tttaagaagg ggaatgtcaa gagatgaggc tgaaccttgg cagggatgga tccttggacc 360

acatcatgta gttgaccctg tcacatagct tggacttcac cttgtgggtg acaggaggcc 420

accagggctg acagtagagg aagaacatgg ccatggaatc cttgggagaa gtggtgtggg 480

ttcattgaaa aggccagggc agaggctgaa agactcatca ggggaatgta gcagtgatcc 540

gcaggggttg tttagggacc agtcatgact gtggcatggg gctgggaaaa tggggccat 599

<210> SEQ ID NO 185
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 185

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taatgatatt attgtatgat cactacacaa catgtctggt tcaggcactt tatgtgtatt 120

aaactatgaa ttccttcaac aaccttataa ggcagatatc actcttagcc ccactttaca 180

gatgaggaaa ccatggccca gagagagcca gtaacttgct ggggaacttg gtttttgagt 240

ggcagagctg ggattcagac ctagaaagtc tggctccaga acccatacac tgatagagtr 300

tatttctgtt caatatttat taaactcctg catgtgtttg acactctgct aggcaccagg 360

gatttaggat ggaaaggaca gtcatttcct tgcctgccct catggagctt ctgatttgtg 420

gatggaaggc atgaacatag gtgtggtggt catggtgcct cccacccatc atgaacttga 480

accaaaacag gaattctttt gtcagttttt tctatcggtt tttggggaag ttttattgga 540

aaaaaaactt ctaaacaaaa gcttaaaaag tatgctttat tgtcttttac ccttattat 599

<210> SEQ ID NO 186
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 186

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gctccagaac ccatacactg atagagtata tttctgttca atatttatta aactcctgca 120

tgtgtttgac actctgctag gcaccaggga tttaggatgg aaaggacagt catttccttg 180

cctgccctca tggagcttct gatttgtgga tggaaggcat gaacataggt gtggtggtca 240

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tggtgcctcc cacccatcat gaacttgaac caaaacagga attcttttgt cagtttttts 300

tatcggtttt tggggaagtt ttattggaaa aaaaacttct aaacaaaagc ttaaaaagta 360

tgctttattg tcttttaccc ttattatcga accagtggaa aatcagaaaa atacaagtgc 420

ttacaccagc aataaaaaaa tatggttctc atcaacacca ccctttgccc cgagccctag 480

agtgtctttc tccaagttgt ctaaatttcc cttcagttcc tgggaccagc tgagaggaca 540

gggagcccac acttggcccc acatgagacc tggttccatt tctctccttg gggcactct 599

<210> SEQ ID NO 187
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 187

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acccttgcc ccgagcccta gagtgtcttt ctccaagttg tctaaatttc ccttcagttc 180

ctgggaccag ctgagaggac agggagccca cacttggccc cacatgagac ctggttccat 240

ttctctcctt ggggcactct acaacttccc actctgcccg ggtcatgtgt ggagctgacy 300

agatacttaa aaacaacaac aacaacaaca acaacaacaa caacaaacaa tgttattttg 360

taagagcagt tttaagttca cagcaaaaat gagtggaaag tagagcattc ccacaggtcc 420

tctctcccca cgtgcgcagc cccggttatc aacacgccca ccagactggt gcatttgtta 480

caactgacgc agctacactg acacgtcatt tccagtgaag tccagagtct gcattagggt 540

tccctattgg ggctgcgcca tttttctcac cagcagtgaa tgagagttct gctgctcca 599

<210> SEQ ID NO 188
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 188

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tggaaagtag agcattccca caggtcctct ctccccacgt gcgcagcccc ggttatcaac 180

acgcccacca gactggtgca tttgttacaa ctgacgcagc tacactgaca cgtcatttcc 240

agtgaagtcc agagtctgca ttagggttcc ctattggggc tgcgccattt ttctcaccar 300

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ggattggacc attccctaac gacatacgat gtggggcacc ttttcaaatg cttacttgca 420

tctgtacatc ttctctggcg aagtgtctgt tcaggtcttt tgcccattgt ttaactgagt 480

tgtgctgacc aggtactttg aggaactcca gacttgtggc tatggcatca tcctggggcc 540

ccataggcca gttcaggagg gtggctggtg agcgatcctg cttgctggcc tgtgcaaaa 599

<210> SEQ ID NO 189
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 189

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caggagtaaa aagaagcaca gaagggacag aggttccagt tcttcttgag gcctgctgtc 180

ccatccttgg gttttgagag acacctctgt gtccttgcag agaattcacc actttgttca 240

aaccagtctg agaaagcttc tttattgtgg tccccaagtg cagctgctgc aatgaccacy 300

gttaacttcc ccgccttggc aaaataactg atactccaaa ctgctaagag tcccaggact 360

gcaccagtta gctattactg tgtaacaaat tgtcccccga tacagcagct tcaaacagcc 420

ataaatattt attacctccc aggttctgag ggccaggcat ctgggagtgg cttggagggg 480

tgtttctggc tcagggtctc atgaggctgc agtcatactg tccctgaggc tgcatcgtct 540

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<210> SEQ ID NO 190
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 190

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cggggtgtgg ggcaggagat tgaagctgca atctttcata acctaagctt ggaagtgcta 120

ttccatcact tctgccacgg gctgctggtc acttggacca tccctgggga aaggaaacta 180

cacagggtgt gaaaaccagg aggcggggct cactgggggt ctctgagaat ctggctacca 240

gcaagatctt gcaggaagtg atggacagcc ccaggtggac gcgtggcata ggggtctgcy 300

gcctcctcct cgtattatct tatcttctga gagctgctcc tgggtgaaca ggtgctcact 360

gcctcttttt ctgggttcac atggacctgg gttagaaagc tgcctctaac atttactagc 420

aagtgacttc tctatgcctc tattttctta tctgcaaaat cgggagaaaa atattgtcct 480

catcgagttt ttctgaacct taaatgcaga gatcttatca gaaagttctt ggccgttgtc 540

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<210> SEQ ID NO 191
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 191

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ggcaaaaaaa aaaaaaaaaa cccaaccaaa aaaaaccccc aaaaaaaccc caacttgaag 120

tggattcagc cacaatgtat tggatggtga acacgaaggg caggaggaag gggggggggt 180

gggggtggta gggaggggcc tggttcaggc cccacaggcc ctaggacgct ggtgccctct 240

ccccctctgg ccacaccctc cagggctctg ctgacccctc cccagcttcc cccctgcaty 300

cgtaccatgg cgggagcagt gcaagcctca cgtctagtag gaagcagcag gagtctttcc 360

cagcattccc caacaagagt ctcattggct gtggttgggg cacatgacag tccctgacca 420

atcactgagg cctgggtctg attggctagg cttgggtcac atggcccact tttggcccag 480

tgggtgaagc cactcttgaa atggatcctg gccaggagga gtcctcctta taggaaagtt 540

gggttacggt tcccagaaga ggtgggaagg gatgctgggt agccagaact gacactggc 599

<210> SEQ ID NO 192
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 192

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gaggctggaa cctggccctg agagacccat tgcctttctc tgttctgtaa cctcttccca 120

tagagatttt tatcctgtaa ccctgtggtc atcaccatgc ctcccattta tgtgcagttc 180

ctatgggctc ctgatgcttt cctggatttc tcccaggaga ggctgttggg tgttggggtg 240

ttggggaaga gaattagtgt tctgcagtct ggagttcact ggtctgcaga ctgctaaaar 300

tctgggggct gcgtctgcca gggatagtgg ctctggctgg tatggggacc aagggcaaaa 360

ggatcagtga tttcagcaga tgcctttgag ccccgagtct ctggctgtgg actagtccag 420

tagaaagagt gtcttggagt gtggcagagt cccagtcccc tgtctttctt actgtcaaaa 480

ccaaggtttg ggcaatcgat gatctagcta aaaaaacgat gtttttcagc ctgtcctttc 540

tgggctcctc ctgtcccaaa cacagatgtg aagcaatgtg cgagaattcc tattctaca 599

<210> SEQ ID NO 193
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 193

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ctttgtcaat tataagtatt gcatatatct tcttctttgt gcctgttctc ttcatttttc 120

ccacagtatc tttggtcata ctaaagtttt ttttgttgtg tgtttttttt tttttacatt 180

tgatacagtt aaattaaatc ttgttttgat tgtacttttt gtgttagttt aatacataat 240

ttcttatctt ggtgtcagaa aggcattcta tcagaattta ttttcaaatt gtatagatty 300

tccgtgtaca gtttggtctt tggctcaact gaaatttatt tctttttgta ggtgtaagga 360

aaggatatat ttttatcttg ttttcctttg taaagccatt tgtccccaat ccatgtattg 420

aattcttttt ctttttttte tacagatata ttcttatata ttgtttccat aaaattcctc 480

tctattttgt cccatcaatc tatttattca tgcactaata ccacacaatt ttaattatga 540

tagttttact gttaatcttt atctttggta tgactctttc tcactcgttc cttccttcc 599

<210> SEQ ID NO 194
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 194

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atttatttct ttttgtaggt gtaaggaaag gatatatttt tatcttgttt tcctttgtaa 120

agccatttgt ccccaatcca tgtattgaat tctttttctt ttttttctac agatatattc 180

ttatatattg tttccataaa attcctctct attttgtccc atcaatctat ttattcatgc 240

actaatacca cacaatttta attatgatag ttttactgtt aatctttatc tttggtatgw 300

ctctttctca ctcgttcctt ccttccctac cttcttttcc tcgtcttcct ttttcaagac 360

cttcttcctg tttttagcac cttaatcatt cacataaatt ttaggattac cttgttaagt 420

tttatgaaat aatctgttgg aattttggtt agacttgcct taattcatac attaactgga 480

gtagaattgt catctttacc atactgagtt ctactcagga gcatgacata tctcttaatt 540

tatttaatgc ttcctttgtg tctttccatg aagatttaga attttctcca taggtcttg 599

<210> SEQ ID NO 195
<211> LENGTH: 599
<212> TYPE: DNA

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 195

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ttttgtccca tcaatctatt tattcatgca ctaataccac acaattttaa ttatgatagt 240

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ttcttttcct cgtcttcctt tttcaagacc ttcttcctgt ttttagcacc ttaatcattc 360

acataaattt taggattacc ttgttaagtt ttatgaaata atctgttgga attttggtta 420

gacttgcctt aattcataca ttaactggag tagaattgtc atctttacca tactgagttc 480

tactcaggag catgacatat ctcttaattt atttaatgct tcctttgtgt ctttccatga 540

agatttagaa ttttctccat aggtcttgca tgtcttttgt tagacttctt cctaggtgc 599

<210> SEQ ID NO 196
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 196

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ttggttgaag gggttatatt aaatcagata aaataaactt ctaggcaagg tgcaataact 120

ggtataaaga ggaacatttc ataaaaaaca taataacaca tgtaataaat tacttaatag 180

caaagggaca ttcataagga agatacaata ggctatatat atatatctgt taatggatct 240

tcaacatgaa tgaagcaaaa tttgacaaaa ttgcagggtg aaaaaatatc cacaaatatr 300

attggaaatt ttagtaccta tctgtcagca attgatagaa caactagaca gaaactgaga 360

gaagacatgg aaaagctaag cataagtatc ctattaactg cctttgttga attgatactt 420

ataaaaatca acatccccaa ggagagaata cacacttttt tcatattcat tatgatggac 480

tatatgctgc accatacatg aaaattgtta ctgttcttgt ctttttccct ctgtgtataa 540

tgtgtctttt tctctggctg ctttcaagat tttctcttta tcacttgttt gattacaat 599

<210> SEQ ID NO 197
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 197

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ggggggtgag gcttagagca tttcccgtgg gtggaaacag tgaacaggcc tctggaatca 180

agctagccca taacctgccc ggggcacagc aagtggtatg gcgagaacag accaagtttt 240

gggtgccgaa taaggatgag gtaaaccagg ggcagagttt tggaatctca gcccaaaggr 300

gtggcctgag tccaaggctg ggggagcatg cacctgctgg ttgctgacac aggtgatcct 360

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gaactttcca gaagtacagg gcaagtttgt gtctaagcaa agctgagccc tctgcccccc 540

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<210> SEQ ID NO 198
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 198

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gcagaacatt cagcccagcc ttgggtgtca ggcatgtgcc tgcctctctg acctcatctg 120

gtggccaggc tgtgggaagg gaaaactgga ggagtctttg ggggctgagc ctctgggcat 180

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tcagggccat ggtgcccagg ctttatggcc atctcttccc tccaggacca gagggaatga 480

gggcctggct cagttggctt ggttgcccaa ctgtggtcat caggagggtg aatgatgtca 540

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<210> SEQ ID NO 199
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 199

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tttttaccaa ctcttggaat caggcctgtt catacatgat ggcattgctg gatctgggga 180

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ttcagtcatc cattcacttg cccattgacc cacccatcca tccatccacc catccatcca 480

accatccatc cacccaccca tccatccatc catccaccca tccatccatc catccatcca 540

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<210> SEQ ID NO 200
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 200

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agcagataaa cagtgaatgc caggaacaga caagtgtgca gggtcagcag atacaagccc 240

cttgtgggaa gggggttttt ctctaagtat cagattcgtc aattactggg taaatttctm 300

atctcttagg acttcccctt tcaataaata ctttcccaga aagtctcacg aaatcaaccc 360

tgggtctaaa aataaggctc tactcccatc ccctgggcat gagtggtccc catgagccca 420

ggtgcatggc ttgaggaagg cactgggcgg tcacaggagt gctttgtgga caaggtgcca 480

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atggtgtggg cagagatctg gcagacagta gtccctactc tcttcctgtc ttgatgagga 540

ggatccgagc tggcccagag aaggggcaag ccttccaggt agagggaata acatgggca 599

<210> SEQ ID NO 201
<211> LENGTH: 73344
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 201

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attgtcatgt taggaggtgg taaaacagta tgtaacccaa aacagagaaa aatggtatta 180

tagaaatggg tcaggtagtt aagaaataaa aacatcagca ctttcctgtg ttttgtggtg 240

tttgcaatat ttgtgagctt tgtaacattc gacttgtgat ttttttcctt ctcattctag 300

taaatattca ggttggtgtc tagttttgta gttgcaattt tgtcttcttt ttctttttct 360

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cacgtctggc taattgtttt tgtatgttta gtagggacag ggtttcacct tgttggtcag 600

gctagtctcg aactcctgac ctcatgatcc acctgcatca gcctcccaaa gtgctgggat 660

tacaggcatg agccactaca cccggcctta tttttcttaa agagcccctg tccagttgtg 720

taagctccag gctccttggc gcctggcttc accccaccct ctcagcatcc cctgcccagg 780

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atcgcttctg tatattttca gaattattgg ttaagccaaa attggattat tgatcattcc 1020

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ccttgcgttg gaccacattt cagtctcaca gcagtgtttg aagatggcta cactgattat 1320

cctgtgttac agataagcaa attgaggcta agagtggcta agcaatacat tcacgatggc 1380

acagctgata tgtagtgaga gttcagtttt gaactcaggt ctgagagccc cattttcatg 1440

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accagccccc actcccaacc actctccttg gctctatttg taaagtgaat tactgcatta 1620

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gtatatctcc cattccacct gctcttctta caaagtaagg tcgacactct ccctttgaga 2280

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cagaagccat gagagataac aaatgatgat tgttgttttg agtgactcca tcttggggca 2700

gtgttattca aacagaataa ccagaacaca tgctgctaat aaagacgtat ctgagactga 2760

gtgatttatg aaggaaagag gtttaattgg ctcacagtcc cacatggctg gggaggcctc 2820

acaatcatgg ctgaaggtga acaaggagca aaatcacgtc ttacatggca gtaggcaaga 2880

cagcatgtgt aggggaactc ccctttataa aaccatcaga tctcaggaga cttattcaca 2940

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ctcccatgat aagtgggaat tatggaagct acaggaatta tgggaattac aattcaagat 3060

gagatttggg tggacataca gtcaaaccat atcaccgttt gtgtgtggaa ggcagaatag 3120

tggcccccaa aaatgtcttc atcctaatcc ctgaaatttg tgaacatgtt aggttacagg 3180

acaaagggga attaaagtca cagatggaat taaggctaat aatcagcagg cctcaagata 3240

gggagaccat cctgaatcat ccagcttggc ccagtgtcat cacagggtcc ttaaaagtgg 3300

aagagaggga gtaagaggag aatcagaggg agttgtgatg gtggaggcaa ggcacagaaa 3360

gatgcagtgt tgctggcttg gaacatggag aaggggcacg agccaggaaa tgctggtggc 3420

ctccagaagc tggaaaaggc aaggaaatga tttgcacccg caggctccag aaggaacctg 3480

gattcaagcc ctgtgagacc tgtcctgacc tctgggactg tagagtgata agtgtctgtt 3540

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The invention claimed is:

1. A method for determining a susceptibility to prostate cancer in a human individual, the method comprising:

analyzing a nucleic acid sample obtained from the human individual to determine the presence or absence of allele G of polymorphic marker rs10896450,

detecting the presence of allele G of polymorphic marker rs10896450 in the sample, and

determining an increased susceptibility to prostate cancer in the human individual by calculating a risk score for the individual which is the product of the risk values for a plurality of factors, wherein one of the factors is a relative risk (RR) or odds ratio of at least 1.1 attributed to the presence of allele G of polymorphic marker rs10896450 in the nucleic acid sample of the individual, wherein the determining is performed using an apparatus comprising:

a computer readable memory;

a processor; and

a routine stored on the computer readable memory; wherein the routine is adapted to be executed on the processor to analyze genotype data with respect to at least polymorphic marker rs10896450, and generate an output based on the genotype data, wherein the output comprises a risk score for the human individual with respect to prostate cancer.

2. A method for determining a susceptibility to prostate cancer in a human individual, the method comprising:

analyzing a nucleic acid sample obtained from the human individual to determine the presence or absence of allele A of polymorphic marker rs11228565,

detecting the presence of allele A of polymorphic marker rs11228565 in the sample, and

determining an increased susceptibility to prostate cancer in the human individual by calculating a risk score for

the individual which is the product of the risk values for a plurality of factors, wherein one of the factors is a relative risk (RR) or odds ratio of at least 1.1 attributed to the presence of allele A of polymorphic marker rs11228565 in the nucleic acid sample of the individual, wherein the determining is performed using an apparatus comprising:

a computer readable memory;

a processor; and

a routine stored on the computer readable memory; wherein the routine is adapted to be executed on the processor to analyze genotype data with respect to at least polymorphic marker rs11228565, and generate an output based on the genotype data, wherein the output comprises a risk score for the human individual with respect to prostate cancer.

3. A method for determining a susceptibility to prostate cancer in a human individual, the method comprising:

analyzing a nucleic acid sample obtained from the human individual to determine the presence or absence of allele A of polymorphic marker rs7947353,

detecting the presence of allele A of polymorphic marker rs7947353 in the sample, and

determining an increased susceptibility to prostate cancer in the human individual by calculating a risk score for the individual which is the product of the risk values for a plurality of factors, wherein one of the factors is a relative risk (RR) or odds ratio of at least 1.1 attributed to the presence of allele A of polymorphic marker rs7947353 in the nucleic acid sample of the individual, wherein the determining is performed using an apparatus comprising:

a computer readable memory;

a processor; and

a routine stored on the computer readable memory; wherein the routine is adapted to be executed on the processor to analyze genotype data with respect to at least polymorphic marker rs7947353, and generate an output based on the genotype data, wherein the output comprises a risk score for the human individual with respect to prostate cancer.

4. A method for determining a susceptibility to prostate cancer in a human individual, the method comprising:

analyzing a nucleic acid sample obtained from the human individual to determine the presence or absence of allele G of polymorphic marker rs10896450,

detecting the presence of allele G of polymorphic marker rs10896450 in the sample,

determining an increased genetic susceptibility to prostate cancer in the human individual attributed to the presence of allele G of polymorphic marker rs10896450 in the nucleic acid sample of the individual, and

performing a prostate Specific Antigen (PSA) test, a Digital Rectal Examination and/or a prostate biopsy on the individual determined to have the increased genetic susceptibility.

5. A method for determining a susceptibility to prostate cancer in a human individual, the method comprising:

analyzing a nucleic acid sample obtained from the human individual to determine the presence or absence of allele A of polymorphic marker rs11228565,

detecting the presence of allele A of polymorphic marker rs 11228565 in the sample,

determining an increased genetic susceptibility to prostate cancer in the human individual attributed to the presence of allele A of polymorphic marker rs11228565 in the nucleic acid sample of the individual, and

performing a prostate Specific Antigen (PSA) test, a Digital Rectal Examination and/or a prostate biopsy on the individual determined to have the increased genetic susceptibility.

6. A method for determining a susceptibility to prostate cancer in a human individual, the method comprising:

analyzing a nucleic acid sample obtained from the human individual to determine the presence or absence of allele A of polymorphic marker rs7947353,

detecting the presence of allele A of polymorphic marker rs7947353 in the sample,

determining an increased genetic susceptibility to prostate cancer in the human individual attributed to the presence of allele A of polymorphic marker rs7947353 in the nucleic acid sample of the individual, and

performing a prostate Specific Antigen (PSA) test, a Digital Rectal Examination and/or a prostate biopsy on the individual determined to have the increased genetic susceptibility.

7. The method according to claim **4**, wherein the step of determining a susceptibility includes calculating a risk score for the individual that includes a relative risk (RR) or odds ratio of at least 1.1 attributed to allele G of polymorphic marker rs10896450 being present in the nucleic acid sample of the individual.

8. The method according to claim **5**, wherein the step of determining a susceptibility includes calculating a risk score for the individual that includes a relative risk (RR) or odds ratio of at least 1.1 attributed to allele A of polymorphic marker rs11228565 being present in the nucleic acid sample of the individual.

9. The method according to claim **6**, wherein the step of determining a susceptibility includes calculating a risk score for the individual that includes a relative risk (RR) or odds ratio of at least 1.1 attributed to allele A of polymorphic marker rs7947353 being present in the nucleic acid sample of the individual.

10. The method according to claim **1**, further comprising assessing at least one non-genetic factor to make a susceptibility assessment, and determining a susceptibility to prostate cancer for the individual from the combination of the at least one non-genetic factor and the presence of allele G of polymorphic marker rs10896450.

11. The method according to claim **10**, wherein the non-genetic factor comprises a measurement of prostate specific antigen (PSA) from the individual.

12. The method according to claim **2**, further comprising assessing at least one non-genetic factor to make a susceptibility assessment, and determining a susceptibility to prostate cancer for the individual from the combination of the at least one non-genetic factor and the presence of allele A of polymorphic marker rs11228565.

13. The method according to claim **12**, wherein the non-genetic factor comprises a measurement of prostate specific antigen (PSA) from the individual.

14. The method according to claim **3**, further comprising assessing at least one non-genetic factor to make a susceptibility assessment, and determining a susceptibility to prostate cancer for the individual from the combination of the at least one non-genetic factor and the presence of allele A of polymorphic marker rs7947353.

15. The method according to claim **14**, wherein the non-genetic factor comprises a measurement of prostate specific antigen (PSA) from the individual.

16. The method according to claim **1** or **4**, wherein the human individual has a Caucasian ancestry, as self-reported by the individual.

17. The method according to claim 2 or 5, wherein the human individual has a Caucasian ancestry, as self-reported by the individual.

18. The method according to claim 3 or 6, wherein the human individual has a Caucasian ancestry, as self-reported by the individual.

19. The method according to claim 1 or 4, further comprising communicating the susceptibility determination to at least one entity selected from the group consisting of the individual, a guardian for the individual, a physician or healthcare worker, a genetic counselor, or an insurer.

20. The method according to claim 19, wherein the communicating comprises making the susceptibility determination available via secure internet interface.

21. The method according to claim 2 or 5, further comprising communicating the susceptibility determination to at least one entity selected from the group consisting of the individual, a guardian for the individual, a physician or healthcare worker, a genetic counselor, or an insurer.

22. The method according to claim 21, wherein the communicating comprises making the susceptibility determination available via secure internet interface.

23. The method according to claim 3 or 6, further comprising communicating the susceptibility determination to at least one entity selected from the group consisting of the individual, a guardian for the individual, a physician or healthcare worker, a genetic counselor, or an insurer.

24. The method according to claim 23, wherein the communicating comprises making the susceptibility determination available via secure internet interface.

25. The method according to claim 1 or 4, wherein the nucleic acid sample is from a human individual who has not been diagnosed with prostate cancer.

26. The method according to claim 2 or 5, wherein the nucleic acid sample is from a human individual who has not been diagnosed with prostate cancer.

27. The method according to claim 3 or 6, wherein the nucleic acid sample is from a human individual who has not been diagnosed with prostate cancer.

28. The method according to claim 1 or 4, wherein the step of analyzing the nucleic acid sample comprises at least one nucleic acid analysis technique selected from: polymerase chain reaction, allele-specific hybridization, nucleic acid sequencing, single-stranded conformation analysis, and electrophoresis.

29. The method according to claim 2 or 5, wherein the step of analyzing the nucleic acid sample comprises at least one nucleic acid analysis technique selected from: polymerase chain reaction, allele-specific hybridization, nucleic acid sequencing, single-stranded conformation analysis, and electrophoresis.

30. The method according to claim 3 or 6, wherein the step of analyzing the nucleic acid sample comprises at least one nucleic acid analysis technique selected from: polymerase chain reaction, allele-specific hybridization, nucleic acid sequencing, single-stranded conformation analysis, and electrophoresis.

31. The method according to any one of claims 1, 2, and 3, wherein the determining of susceptibility is performed using a computer-readable medium on which is stored:

an identifier for the at least one polymorphic marker;

an indicator of the frequency of at least one allele of the polymorphic marker in a plurality of individuals diagnosed with prostate cancer; and

an indicator of the frequency of the at least one allele of the polymorphic marker in a plurality of reference individuals.

32. The method according to any one of claims 4, 5, and 6, wherein the determining of increased genetic susceptibility is performed using an apparatus, the apparatus comprising:

a computer readable memory and a processor; and

a routine stored on the computer readable memory; wherein the routine is adapted to be executed on the processor to analyze marker information for at least one human individual with respect to the polymorphic marker, and generate an output based on the marker information, wherein the output comprises a risk measure of the polymorphic marker as a genetic indicator of susceptibility to prostate cancer for the individual.

33. The method according to claim 32, wherein the routine further comprises an indicator of the frequency of at least one allele of the at least one polymorphic marker in a plurality of individuals diagnosed with prostate cancer, and an indicator of the frequency of the at least one allele of the polymorphic marker in a plurality of reference individuals, and wherein a risk measure is based on a comparison of allelic status of the at least one marker determined for the human individual from the sample and the indicators of the frequency of the at least one allele in the pluralities of individuals.

34. The method according to claim 33, wherein the risk measure is characterized by an Odds Ratio (OR) or a Relative Risk (RR).

35. The method according to any one of claims 1-3, further comprising measuring Prostate Specific Antigen or performing Digital Rectal Examination on a subject identified as having increased genetic susceptibility to prostate cancer.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,697,360 B2
APPLICATION NO. : 12/315114
DATED : April 15, 2014
INVENTOR(S) : Steinunn Thorlacius et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page:

Item (75), in Line 2, "Reyjavik (IS)" should be -- Reykjavik --.

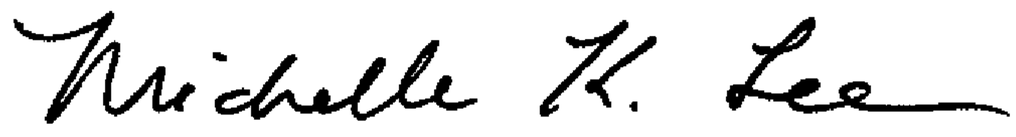
Item (75), in Line 3, "Reyjavik (IS)" should be -- Reykjavik --.

In the Claims:

Column 316, line 13, Claim 31, "for the at least one" should be -- for the --.

Column 316, line 33, Claim 33, "of the at least one" should be -- of the --.

Signed and Sealed this
Second Day of June, 2015



Michelle K. Lee
Director of the United States Patent and Trademark Office